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# DEDICATION

I dedicate this work to my husband, Jasdev Sawhney, and my son Kabir Sawhney for their support and patience; and to my sister and mother (Aarti and Kiran Sachdev) who have supported me by coming to England and providing me with time to write.

# ACKNOWLEDGEMENTS

I wish to particularly acknowledge my supervisor Dr Neil Wright for his help, support, patience and guidance during my PhD. Thank you, Neil for bearing with me and always making yourself available often at short notice.

I would like to thank Professor Nick Bishop and Dr Jerry Wales for their advice and help.

I would also like to thank Professor Paul Dimitri for all his support and guidance particularly focusing on the bone aspects of the project.

Thanks, are also due to Dr Lindsey Reece, who delivered the lifestyle intervention part of the study.

I would also like to thank Dr Anuja Natarajan who referred several patients from her endocrine clinic to assess eligibility, several whom took part in the eventual trial.

I would also like to thank Ellie Cousins, Kabir’s babysitter for her help.

Most importantly, I would like to thank the BOB Participants and their families without whom, this study would not have happened. I thank them for their commitment and time and their willingness to try a treatment that is not well established for young people. The participants in this study include:

# Statement of attribution

Mrs Joy Thorpe, Mrs Anne-Marie and Mrs Elzene Kruger carried out the DXA scan at the 3 timepoints at the radiology department at Sheffield Children’s Hospital. Paper copies of the outputs were provided to PS who then entered the data into an excel spread sheet and reviewed the results and discussed any issues identified.

Dr Mike Thompson, consultant paediatric gastroenterologist placed and removed the intragastric balloons under GA in theatre at Sheffield Children’s Hospital.

PS observed sessions at Claremont hospital with Mr Roger Ackroyd, bariatric surgeon to develop a protocol for balloon insertion and removal and pre-and post care in conjunction with the bariatric and gastroenterology nurses.

Professor Paul Dimitri provided advice regarding the bone aspects of the study and which bone markers were most likely to result in change following weight loss and therefore may be best to measure at the three time points.

Jenny Jones, biochemist at UCLH carried out the analysis for the incretins, ghrelin and bone markers. Standardised assays were used and PS was not involved in choosing which assays were used.

Statistical advice was provided by Dr Richard Jacques for the study and analysis done for some of the data as detailed below.

PS analysed the weight, anthropometric and metabolic data including the incretins, ghrelin, bone markers. These were analysed using paired T tests in excel. Correlations were done between change in weight and change in metabolic markers using pearson’s correlation also in excel. Data was expected to be normative.

Dr Richard Jacques analysed the DXA and HRpQCT data and looked at correlations between the change in this data and change in the bone markers.

DR M Paggiossi and Selina Bratherton at Northern General Hospital carried out the HRpQCT scans at the 3 time points.

PS attended two tutorials with them to improve her understanding of the Scanco machine and the process of image acquisition.

Dr Lindsey Reece delivered the life style intervention programme at Sheffield Hallam Uinversity. PS and LR met regularly before the patient was recruited and during the time the balloon was insitu to discuss progress and coordinate participant visits.

PS also organized and chaired quarterly meetings with the wider study team (NPW, JKW, RJC, MAT) between 2012-2015.

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12. Publications from the study

12a) Sachdev P, LJ Reece, Natarajan A, RJ Copeland, M Thomson, JK Wales and NP Wright. Intra-gastric balloon as an adjunct to lifestyle support in severely obese adolescents; impact on biomedical outcomes and skeletal health. 2017; International Journal of Obesity 1-4

12b) LJ Reece, P Sachdev, RJ Copeland, M Thomson, JK Wales and NP Wright. Intra-gastric balloon as an adjunct to lifestyle support in severely obese adolescents; impact on weight, physical activity, cardiorespiratory fitness and psychosocial well-being. 2016; International Journal of Obesity 1-7

12c) Reece LJ, Copeland RJ, Sachdev P, Thomson M, Wales JK et al. (2014) Protocol for: The Use of Intra-Gastric Balloons as an Adjunct to a Lifestyle Support Programme to Promote Weight Loss in Severely Obese Adolescents. J Child Adolesc Behav 2: 173 doi: 10. 4172/2375-4494. 1000173

13) Correlations between bone markers and changes in DXA and HRpQCT

# Publications from this study

Sachdev P, LJ Reece, Natarajan A, RJ Copeland, M Thomson, JK Wales and NP Wright. Intra-gastric balloon as an adjunct to lifestyle support in severely obese adolescents; impact on biomedical outcomes and skeletal health. 2017; Int J Obes (London).2018 January; 42 (1): 115-118

LJ Reece, P Sachdev, RJ Copeland, M Thomson, JK Wales and NP Wright. Intra-gastric balloon as an adjunct to lifestyle support in severely obese adolescents; impact on weight, physical activity, cardiorespiratory fitness and psychosocial well-being. 2016; Int J Obes (London). 2017; 41(4): 591-597

Sachdev P, Makaya T, Marven S, Ackroyd R, Wales, Wright N. Bariatric surgery in severely obese adolescents-A single centre experience. *Archives of Disease in Childhood.* 2014; 99: 894-898

Reece LJ, Copeland RJ, Sachdev P, Thomson M, Wales JK et al. (2014) Protocol for: The Use of Intra-Gastric Balloons as an Adjunct to a Lifestyle Support Programme to Promote Weight Loss in Severely Obese Adolescents. J Child Adolesc Behav 2: 173 doi: 10. 4172/2375-4494. 1000173

# Published abstracts from this study

BSPED 2013, BSPED 2015, BSPED 2016, ESPE 2015 AND 2016 (BSPED-British Society of Paediatric Endocrinology and Diabetes, ESPE-European Society of Paediatric Endocrinology)

BSPED Report –https://www.bsped.org.uk/media/1270/bsped\_report-bow-study-2017\_sachdev.pdf

BSPED Research Award (£15000) awarded in 2012

# Oral presentations

1.**Biomedical outcomes of weight loss associated with intragastric balloon therapy in severe adolescent obesity. (Oral) BSPED 2016 Nottingham**

**Background:** Severe obesity in childhood is associated with significant morbidity including systolic hypertension, fatty liver, obstructive sleep apnoea, dyslipidemia and type 2 diabetes. Evidence that even small changes in BMI SDs bring about significant clinical benefit is strong.

**Objectives:** To assess the impact of weight loss associated with intragastric balloon therapy supported by a life style programme on biomedical outcomes (glucose metabolism, blood pressure, lipid profiles) in severely obese adolescents and to observe any changes in incretin, ghrelin and adipokine hormones.

**Methodology:** A 2-year cohort study of 12 adolescents (BMI 3. 5 SD, Tanner stage 4 or above) following 6 months intragastric balloon placement. Subjects underwent anthropometry, oral glucose tolerance test, measurement of basal and stimulated incretins and adipokines at 0, 6 and 24 months.

**Results**: Mean weight loss at 6 months was 7. 1 kg, (-27,12.8), p value0. 005), (5% body weight) but weight loss was sustained in only 20% patients at 2-years. Insulin area under the curve following OGTT improved at 6 months (P0. 05). As individuals tended to regain weight following balloon removal HOMA scores and fasting insulin levels increased but Insulin AUC remained below pre-intervention levels. There was also a fall in HBA1c at 6 months that was maintained despite weight regain (P0. 005). There was a significant increase in fasting GLP-1 over the 24 months (P0. 04). The area under the curve (AUC) for GLP-1 also improved at 24 months despite weight regain. The significant drop in GIP at 6 months (P0. 001) was not sustained at 24 months. We noted moderately strong inverse correlations between percentage weight loss and change in GLP-1 AUC (r=0. 45) and ghrelin (r=0. 51) at 6 months. Clinically relevant improvements were also seen in blood pressure, liver function at 6 months.

**Conclusion**: Short-term weight loss and clinically relevant improvement in obesity related complications were seen after 6 months of intragastric balloon therapy. Benefits were sustained in some patients but not the majority at 2 years.

**DOI:** 10. 1530/endoabs. 45. OC8. 5

2.Impact of Intragastric Balloon placement on cortical and trabecular microarchitecture and bone strength in severely obese adolescents. (Oral) ESPE 2016

3.Impact of intragastric balloon bariatric intervention on skeletal microstructure and strength in severely obese adolescents - a longitudinal study (oral) BSPED 2015

4. A pilot study of the acceptability and efficacy of intragastric balloons in severe adolescent obesity. British Society of Paediatric Diabetes and Endocrinology, Brighton 2013 (oral)

*5.* **The impact of intragastric balloon placement supported by a lifestyle intervention programme on cortical and trabecular microstructure and strength in severely obese adolescents**

**Background:** The effect of profound weight loss following obesity surgery on skeletal microarchitecture and strength in adolescents has not been studied. Obese children are at an increased risk of fracture and childhood obesity leads to reconfiguration of trabecular bone without augmenting bone strength.

**Objectives:**  To examine the impact of weight loss following 6 months treatment with an intragastric balloon supported by a lifestyle intervention programme on cortical and trabecular bone microstructure and bone strength in obese adolescents.

**Methodology:**  We recruited 12 adolescents aged 13. 8–16. 8 years, BMI >3. 5 S. D. Tanner stage 4/5) to undergo intragastric bariatric balloon placement. Serial distal radial and tibial high resolution pQCT (peripheral quantitative computed tomography) imaging, subtotal body and lumbar spine (LS: L1 to L4) DXA was performed at baseline and 6 months. HRpQCT measures of microstructural properties included trabecular number (Tb. N, 1/mm), trabecular thickness (Tb. Th, mm), trabecular separation (Tb. Sp, mm), and cortical thickness (Ct. Th, mm). Biomechanical parameters were defined by miocrofinite element analysis. Results are expressed as (mean difference, 95%CI, significance (p value)).

**Results:** Weight SDS and BMI SDS decreased significantly (−0. 38 (−0. 62, −0. 13) and −0. 27 (−0. 44, −0. 10) respectively, P=0. 005). Total body bone mineral content (BMC), LS BMC and LS bone area all demonstrated age appropriate increases following the balloon removal. Cortical volumetric BMD (vBMD) 14. 0 mg/cm3 (8. 2, 19. 7), P<0. 001) and cortical perimeter size (4. 0 mm (0. 5, 7. 5), P=0. 029) increased at the radius. Cortical area (2. 4 mm2 (0. 1, 4. 7), P=0. 042), cortical BMD (11. 1 mg/cm3 (4. 1, 18. 0), P=0. 006) and cortical thickness (0. 02 mm (0. 001, 0. 04), P=0. 042) increased at the tibia. Paradoxically, total bone area at the radius diminished (−6. 1 mm2 (−8. 9, −3. 2), P=0. 001). Bone stiffness and estimated ultimate failure load did not significantly change following surgery.

**Conclusions:** There was no evidence of skeletal deterioration following intragastric balloon insertion despite a reduction in BMI SDS. Total body and regional bone accretion continued with the greatest gains in cortical bone. In the short term, balloon bariatric surgery does not cause bone loss in adolescence.

*Endocrine Abstracts* (2015) **39** OC6. 9 | DOI: [10. 1530/endoabs. 39. OC6. 9](https://doi.org/10.1530/endoabs.39.OC6.9)

**2 abstracts included above as examples.**

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# GLOSSARY OF TERMS

**Anthropometry**

LM Lean mass

TFM Truncal fat mass

TW3 Tanner Whitehouse (bone age)

WHR Waist Hip ratio

**Biochemical terms**

CTx C telopeptide Collagen Crosslink

DKK-1 Dickkopf-1

ELISA Enzyme-Linked Immunosorbent Assay

GIP Glucose dependent insulinotrophic polypeptide secreted by K cells in the proximal small intestine

GLP-1 Glucagon like peptide-1 secreted by the L-cells of the small distal intestine

NTx N telopeptide Collagen Crosslink

OPG Osteoprotegerin

P1NP Aminopropeptide of type 1 collagen

RANK-L Receptor Activator of Nuclear Kappa B Ligand

RIA Radioimmunoassay

**Bone Densitometry**

aBMD Areal Bone Mineral Density

BA Bone Area

BMAD Bone Mineral Apparent Density

BMC Bone Mineral Content

Ct.Ar Cortical Area

Ct.BMD Cortical BMD

Ct.Po Cortical Porosity

Ct.Po.Dm Mean cortical pore diameter

FM Fat Mass

F.ult Ultimate failure load

LM Lean Mass

S Stiffness

Tb.Ar Trabecular area

Tb. BMD Trabecular BMD

(Tb.F/TF) distal % load carried by the trabecular bone (distal)

(Tb.F/TF) proximal % load carried by the trabecular bone (proximal)

Tb. N Trabecular number

Tb.Sp Trabecular separation

Tb.Th Trabecular thickness

TBLH Total Body Less Head

vBMD Volumetric Bone Mineral Density

**Equipment**

DXA Dual energy x-ray absorptiometry

HRpQCT High Resolution peripheral quantitative computed tomography

MR Magnetic Resonance

**Miscellaneous**

BMI Body Mass Index

BOB Balloons in Obesity Study

CHD Coronary Heart Disease

IGB Intragastric balloon

MEND Mind, Exercise, Nutrition, Do IT

NICE National Institute for Health and Care Excellence

OSCA Obesity Services in Children and Adolescents

QoL Quality of Life

RY-GB Roux-en Y gastric bypass

SHINE Self Help Independence Nutrition Exercise programme

SHOT Sheffield Obesity Trial

SUFE Slipped upper femoral epiphysis

**Statistics**

SD Standard Deviation

SDS Standard Deviation Scores

# SUMMARY

**Rationale and Introduction:** A small number of young people (aged between 12-18 years) have very severe obesity typically weighing up to 24 stone (150 kg). Such individuals can suffer significant obesity related health problems whilst still young. Importantly, such individuals also suffer significant psychosocial effects including poor self-esteem, high rates of depression & poor school attendance. This has an adverse effect on their quality of life. As adults, such individuals would be eligible for gastric band or bypass surgery in line with NICE guidance. NICE guidance makes provision for surgery in adolescents in exceptional circumstances but there is reluctance amongst paediatricians to consider this. Weight and behaviour management programmes and pharmaceutical treatment for obesity, are of limited benefit in this group.

We therefore proposed a feasibility study of intragastric balloons (supported by a lifestyle program) to help severely obese adolescents lose weight. The balloon is placed in the stomach endoscopically (in adults awake - in children under anaesthetic which is routine for such a procedure) and inflated - it can be left for 6 months. The rationale is that in adults, balloons have been shown to promote a change in BMI of 4. 0 - 9. 0 kg/m2 and a mean weight loss of 17. 8 kg (approximately 3 stone). But in adults, because of concerns that individuals will subsequently regain weight, banding or bypass surgery is often preferred. However, in adolescents’ balloons may provide a more acceptable and cost-effective option than surgery - balloons are temporary rather than permanent. The risk of a serious complication is much lower at 0. 07% compared to bariatric surgery (mortality approximately 0. 5%). Children are more amenable to lifestyle change and by using balloons to “kickstart” weight loss, supported by a lifestyle management programme; we can provide a platform for longer-term improvement in their weight.

We planned to look over a 2-year period at the efficacy and acceptability of the intragastric balloon supported by a life style intervention in severely obese adolescents to support weight loss.

We also explored the impact of rapid weight loss on the young peoples’ health in terms of their risk of diabetes, high blood pressure, and cholesterol levels. One of the worries about rapid weight loss is the impact on the growing skeleton. Therefore, we also performed DXA scans at the 3 time points, before balloon insertion, after balloon removal and at 24 month follow up. We measured both total body and lumbar spine bone mineral density and bone mineral content. Increasingly, the literature suggests that DXA does not describe the whole picture in terms of fracture risk. We therefore also performed HRpQCT to look at changes in bone density, microarchitecture and bone strength.

**Objectives:** i) To assess the efficacy of the intragastric balloon (*in situ* for 6 months) supported by a lifestyle intervention to promote weight loss in severely obese adolescents. ii) To assess the impact of the weight loss on biomedical outcomes such as glucose metabolism, lipid profiles, bone density and architecture, and on psychosocial health.

**Methods:** 12 severely obese young people who met inclusion criteria (BMI SDS>3. 5, Tanner stage> 4) were recruited for the project and the balloons were inserted between February–August 2013. All balloons remained in situ for a mean of 26 weeks based on manufacturer’s recommendations and all balloon removals were completed by March 2014.

**Results**: The intra-gastric balloon was well tolerated and there were no early balloon removals. Minor Side-effects such as nausea and vomiting were common.

Results showed that the intra-gastric balloon is effective in the short term with a mean weight loss of 7 kg (SD 7.13) from baseline (5% of initial body weight which is considered clinically significant) experienced by the cohort. Ten out of twelve young people lost weight in the 6 months while 2 of the participants lost weight in the first few weeks but put it back on. There were no serious complications

Only 2 of the young people continued to lose weight at follow up 18 months’ post balloon removal.

There were clinically significant improvements in markers of insulin glucose metabolism at 6 months (AUC insulin), and some of these were sustained at 2 years (HBA1c) inspite of the weight re gain. Clinically relevant improvements were also seen in blood pressure, and liver function at 6 months. Some of the more mechanistic work to explore potential hormone mediators such as the adipokines (leptin/adiponectin), and ghrelin did not show any significant change post intervention.

However, the incretin hormone GLP-1 showed significantly increased fasting levels at 6 months and AUC remained higher than baseline even at 24 months. The significant drop in the other incretin GIP at 6 months (p 0. 001) was not sustained at 24 months.

The significance of these findings is unclear and more work is needed to delineate cause/effect.

The TBLH BMC, L1-L4 BMD, L1-L4 BMC, L1-L4 BA all showed a significant increase at 6 months despite a mean reduction of 5% in weight and 2.1 % reduction in TBLH Fat mass (p<0.05). TBLH BMD and L1-L4 BMD z scores remained above baseline at 6 months following weight loss and at 2 years following subsequent weight regain.

Cortical BMD (14. 0 mg/cm3 (8. 2, 19. 7), P<0. 001) and cortical perimeter size (4. 0 mm (0. 5, 7. 5), P=0. 029) increased at the radius. Cortical area (2. 4 mm2 (0. 1, 4. 7), P=0. 042), cortical BMD (11. 1 mg/cm3 (4. 1, 18. 0), P=0. 006) and cortical thickness (0. 02 mm (0. 001, 0. 04), P=0. 042) increased at the tibia. Paradoxically, total bone area at the radius diminished (−6. 1 mm2 (−8. 9, −3. 2), P=0. 001). Bone stiffness and estimated ultimate failure load did not significantly change following surgery. At 2 years, gains in tibial cortical area, cortical BMD and cortical thickness continued with increase in bone stiffness and strength at both tibia and radius.

We also studied a variety of bone markers –both bone formation (Osteocalcin, P1NP, no significant change seen) and resorption markers (OPG, RANK-L, DKK-1, Urine CTX, Urine NTX) to see if there was any change pre-and post intervention and at 18 month follow up. Significant decreases were seen in Urine NTX at 6 months at balloon removal (p=0.001) and this decrease continued at 24 months (p=0.003) despite weight regain.

**Conclusions:** In conclusion, the balloon was well tolerated in this group of young people. Short-term weight loss and clinically relevant improvement in obesity related complications were seen after 6 months of intragastric balloon therapy. At 2 years, benefits were sustained in some patients but not the majority.

There was a significant variation in outcomes which needs exploring further to try and delineate factors leading to success/failure and using these to tailor options in severely obese adolescents.

There was no evidence of skeletal deterioration following intra-gastric balloon insertion despite a reduction in BMI SDS. Total body and regional bone accretion continued with the greatest gains in cortical bone. In the short term, balloon bariatric surgery does not cause bone loss in adolescence.

# A SUMMARY OF THESIS CONTENTS

**Chapter 1**

Introduction outlines the childhood obesity epidemic, describes the category of severe childhood obesity, its estimated prevalence, it’s health consequences, and current management strategies and the lacunae in these.

**Chapter 2**

Traces the history of the use of intragastric balloons in adults, the evidence relating to their efficacy, their impact on comorbidities and limited use in adolescents. It also explains the objective of this thesis.

**Chapter 3**

While the main objective of this thesis is to explore the efficacy and acceptability of IGB as defined by change in weight and BMI, the secondary outcomes include change in metabolic parameters (insulin glucose metablism, blood pressure and cholesterol) following weight loss.

This chapter provides a background of the parameters we chose to measure, what changes are expected in obesity and after weight loss.

We also measured adipokines, incretins and ghrelin on an experimental basis to get some understanding of how these change with a temporary procedure such as a balloon and if these changes can explain some/if any health benefits seen after weight loss.

**Chapter 4**

The focus of this chapter is the relationship between fat and bone.

This chapter describes the impact of both obesity and weight loss on bone in adults and children of different ages and pubertal staging. One of the concerns associated with rapid weight loss is related to its impact on the growing skeleton. We also describe the bone markers involved in bone formation and resorption, the changes in which may explain the bone loss described after weight loss in some studies. There is also a brief description of DXA and why we chose to complement this with the use of HRpQCT.

**Chapter 5**

Describes how the study was conducted over the 2 years including the groundwork involving ethics, R&D approval, plan for statistical analysis, radiation protection report, funding, recruitment, balloon insertion, removal and follow up and the monitoring involved at different time points.

**Chapter 6**

Results and Discussion pertaining to the recruitment process, feasibility and Initial demographics and anthropometry of the young people and their engagement with the programme (both medical appointments and lifestyle intervention).

**Chapter 7**

Results and Discussion pertaining to weight loss, change in anthropometric measures.

A Description of the changes in the metabolic parameters at 6 months after weight loss and at 2 years after weight regain in the majority. This chapter includes results related to adipokines and incretins and any significant correlations related to this.

**Chapter 8**

Results and discussion regarding changes in DXA and HRpQCT at 6 months and 24 months. This chapter also includes bone marker results and any significant correlations.

**Chapter 9**

Feedback and future work/directions

## Introduction

### The Obesity Epidemic

#### Incidence

We are in the throes of an epidemic of childhood obesity. Currently, 30-45 million children aged 5-17 years are classified as obese. (1)Studies over the last three decades have shown the frequency of overweight children and childhood obesity to be on the increase – some figures suggesting a tripling of numbers over the last 30 years (2). However, there is some recent evidence to suggest that this may be plateauing (3).

The Health and Social Care Information Centre statistics from 2016 showed that 1/5 of children in reception and 1/3rd of children in Year 6 were obese or overweight (Overweight defined as body mass index (BMI) >85th centile, Obesity defined as BMI>95th centile, UK 1990 Growth Standards)(4) .

As in previous years, there was a strong positive correlation between deprivation and the prevalence of obesity with children in most deprived areas being twice as likely to be obese. Obesity was also significantly higher in urban rather than rural communities. However, Foresight’s extrapolations in his report which aims to look at ways of tackling obesity in the UK in the longer term, suggest that only 30% of girls and 45% of boys under 20 will be a healthy weight by 2050(5).

#### Definition, Classification and grading in adults and children

The epidemic of obesity is universal and over 300 million people are considered obese with a resultant impact on QoL and life expectancy due to the associated co-morbidity. Levels of obesity continue to rise with a peak seen in the 5th to 7th decade. The table below shows the classification of obesity based on BMI (Body Mass Index) in adults with increasing risk of Type 2 diabetes and cardiovascular disease seen with higher BMI.(6)

Table - Classification of obesity in adults

|  |  |
| --- | --- |
| **Classification** | **BMI (kg/m2)** |
| Healthy weight | 18. 5–24. 9 |
| Overweight | 25–29. 9 |
| Obesity I | 30–34. 9 |
| Obesity II | 35–39. 9 |
| Obesity III (Morbid) | 40 or more |

The values of > 25 kg/m2 for overweight and >30 kg/m2 for obesity cannot be applied to children as they are still growing. Therefore, BMI centile charts or Z scores are needed to assess obesity during childhood. Gender specific BMI reference curves were used in the National Health and Nutrition Examination survey (NHANES1) with the 85th and 95th centile used as cut offs for overweight and obesity respectively (7)

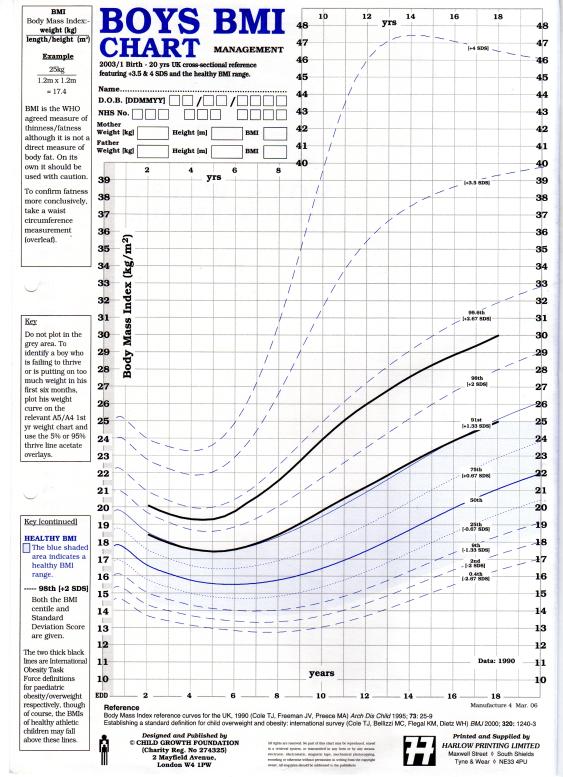
The first BMI reference curves were produced by Cole et al in 1990 using the UK population(8).

Median BMI stabilizes at about 15 kg/m2 between the age of 4-6 years followed by a gradual rise into adolescence and adulthood (see Figure 1 & 2).

Figure 1 - Body Mass Index (BMI) percentile charts for girls from the Child Growth Foundation, United Kingdom (Cole, Freeman et al. 1995)



Figure 2 -Body Mass Index (BMI) percentile charts for boys from the Child Growth Foundation, United Kingdom (Cole, Freeman et al. 1995)



Using BMI is the most practicable definition of childhood obesity inspite of its limitations as it is easily obtained in clinical settings though measures such as skin-fold thickness or waist circumferences may co-relate better with percentage of body fat and co-morbidities(9) BMI SDS is used rather than crude BMI to take into account that it changes with age/growth.

Though, the 85th and 95th centile continue to be used in epidemiological studies as cut off points (thresholds) for childhood overweight and obesity respectively.

However, for clinical use NICE (2006) recommends using BMI>91st centile and BMI >98th centile (2 SDS above the mean) to define overweight and obesity(10).

There are no agreed definitions for extreme obesity in childhood. The SIGN (Scottish Intercollegiate Guidelines Network) guidance defines very severe obesity as >3. 5 SDS above the mean for age and sex and extreme obesity as >4. 0 SDS above mean(11).

The recent OSCA (Obesity Services in Children and Adolescents) review suggests that any child with a BMI > than 3. 5 SD above the mean be regarded as having extreme obesity(12). This is equal at 18 years of age, to the adult definition of class III obesity or BMI >40 kg/m2.

Table 2 summarises the Classification of obesity in children and young people

Table - Classification of obesity in children and young people

|  |  |  |
| --- | --- | --- |
| **Classification** | **BMI centile** | **BMI SDS** |
| Healthy weight | 9th -91st centile | -1.33 SDS to +1.33 SDS |
| Overweight | >85th centile (91st centile in epidemiological studies) | +1.33 SDS |
| Obesity | >95th centile (98th centile in epidemiologicsal studies) | + 2.0 SDS |
| Severe obesity | >99.6th centile | + 2.67 SDS |
| Very severe obesity |  | SIGN +3.5SDS |
| Extreme obesity |  | +3.5 SDS OSCA (SIGN + 4.0 SDS) |

The number of children at the extreme end of the spectrum is unclear, however, a recent estimate of severe obesity in England (BMI >99. 6th centile) using the National child measurement programme data has put these numbers at 1. 9% for girls and 2. 3% for boys in the 4-5-year age group with increases to 2. 9% for girls and 3. 9% for boys in the 10-11-year category.

These numbers may be much higher by the time the children reach mid to late adolescence. With the child population of the UK approaching 12 million, extrapolating these percentages would give an estimate of 400,000 children with severe obesity. It was also noted in this study that black ethnicity was worst affected compared to Asian, mixed, White, and Chinese groups. The prevalence of severe obesity was also higher in those living in the most deprived areas (13). The most recent statistics from the National Child Measurement Programme for England for 2018/2019 showed that the prevalence of severe obesity in children in year 6 was 4.4 percent and it was 4 times more prevalent in areas of maximum deprivation(14)

In comparison, the number of severely obese young people is estimated to be 2 million in the USA(15). Although numbers in the UK are not as large as the USA, they are also the fastest growing group with (3) a lack of services to address their physical and emotional needs.

The aetiology of obesity is complex and not fully understood but environment, cultural issues, changes in lifestyle such as increased intake of fat and calories with decreased physical activity have all played an important role. Although genetic susceptibility may play a role, lifestyle and behavioural factors are more important. Habits established as children and adolescence are likely to continue into adulthood and therefore it is even more important to address these whilst still young(16).

Obesity has significant health implications, both in the short and long term as discussed below.

#### Health and psychosocial repercussions of childhood obesity

Being overweight or obese contributes to significant physical, mental and emotional morbidities (17). These are summarised in ***Figure 3***.

Figure 3 - Physical and Psychosocial consequences of obesity

**Metabolic and cardiovascular:**

Impaired glucose tolerance is seen in a quarter of children and young people with severe obesity, which predicts the risk of development of both diabetes as well as cardiovascular disease(18). Increased arterial wall thickness and endothelial dysfunction is seen in severely obese young people suggesting that obesity induced atherosclerosis starts in childhood (19).

A recent systematic review and meta-analysis of cardio-vascular risk factors in healthy children and their association with BMI which included almost 50,000 children showed that both systolic and diastolic BP was significantly higher in obese children as were fasting insulin and insulin resistance(20). Thus, risk factors for CHD are already present in young people with obesity.

Baker et al in a large study with 5 million person-years of follow up concluded that higher BMI in childhood has been associated with increased risk of CHD, both fatal and non fatal in adulthood(21). The associations were stronger in boys compared to the girls and increased, in both sexes as the children got older.

Must et al provide a comprehensive overview of the immediate, intermediate and long-term consequences of childhood obesity particularly focussing on the severe end of the spectrum(22).

**Respiratory:**

A much more common problem, asthma, is seen in 30% of obese children. Reducing childhood obesity is postulated to be one of the few preventable risk factors related to developing asthma. (23) Sleep disorders, another pulmonary consequence of obesity are seen in between 30-90% of young people with severe obesity and have also been linked to problems with learning and memory due to excessive day time sleepiness. Obstructive sleep apnoea (characterized by snoring, partial and complete obstruction of the airway) is also being linked with cardiovascular disease with changes in blood pressure, arterial stiffness and ventricular function(24).

**Psychosocial:**

The medical consequences of severe obesity are thus well documented but the psychosocial implications of such a degree of overweight in adolescence are often overlooked. Indeed, many children report social rather than health concerns as the key driver to considering weight loss. Such children frequently require support from child and adolescent mental health services (CAMHS) and approximately 30% have depression (25, 26). Many of these individuals have very low self-esteem(27). They are frequently a target for bullying and many simply drop out of school. Not surprisingly, studies have shown that obesity can have an adverse influence on college admission rates in girls(28). Overall health related Qol in severely obese adolescents is lower than normal weight children and is similar to children with cancer (29) and understanding this is key to planning services and treatment options for these young people.

**Polycystic ovarian syndrome:**

Polycystic ovarian syndrome (PCOS) can be difficult to diagnose in adolescents as the pathophysiology of obesity and adolescence can be similar. In a cross sectional study of 49 obese post menarche girls, the incidence of PCOS varied between 18.4 to 26.4 percent depending on the criteria used which is much higher than that quoted in adult literature . (30). A meta analysis in 2017 showed that metabolic disorders in adolescent PCOS are worsened if obesity is also present. Obese adolescents with PCOS have lower SHBG, and HDL-C and higher leptin, fasting insulin, triglycerides, LDL-C and testosterone compared to their non-obese counterparts with PCOS. Thus, obesity management in PCOS is crucial due to the exacerbation of cardiovascular risk factors.(31)

**Obesity related cancers**

Increased BMI predisposes to several site-specific cancers. Using primary care data of patients in the Clinical Practice Research Datalink, associations were studied between BMI and 22 of the most common cancers in the UK which found that 41 percent of uterine and >10 percent of gall bladder, kidney, liver and colon cancers were the result of excess weight. (32) The study concluded that a 1 kg/m2 increase in the population BMI resulted in 3800 additional patients developing one of ten cancers each year.

A recent study looking at cancer incidence trends in the US for 30 cancers including 12 obesity related cancers in young adults aged 25-49 years showed that 6 of these (multiple myeloma, colorectal, uterine corpus, gall bladder, kidney and pancreatic) showed a steeper rise in younger people. This study was comprehensive covering almost 2/3rds of the US population.(33).

**Other:**

Orthopaedic problems such as Blount’s disease and slipped capital femoral epiphysis, as well as neurological problems such as pseudo-tumour cerebi are much more likely in young people with severe obesity. Steatohepatitis is seen in almost half of severely obese young people with the most severe cases leading on to fibrosis and cirrhosis of the liver(22).

The epidemic of childhood obesity is particularly worrying not due to just the effects of obesity in childhood but also because obesity in childhood will affect future adult health.

The majority of children who are obese and remain obese by school-age will become obese adults (34) (35) with a consequent decrease in life expectancy of anywhere between 5 to 20 years (36-38). Thus, childhood obesity and its management is a significant health concern, due to both its medical as well as financial implications for the National Health Service (NHS) in the UK.

#### Review of management of paediatric obesity

The National Obesity Observatory’s report on the economic burden of obesity (2010) quoted the estimates of the direct National Health Service (NHS) costs of treating overweight and obese individuals, and related morbidity in England as ranging from £479. 3 million in 1998 to £4. 2 billion in 2007. The estimated indirect costs (arising from the impact of obesity, for example due to a loss of productivity) ranged from £2. 6 billion to £15. 8 billion (39) The Foresight report estimates that by 2050 these wider costs to society and business will estimate £50 billion per year(40).

#### Lifestyle interventions

Lifestyle modification programmes remain the first line therapy in managing paediatric obesity (10). Various national lifestyle programmes have been established to try and tackle obesity such as MoreLife, Watch IT and MEND.

Local examples include SHINE (Self Help Independence, Nutrition and Exercise) in Sheffield, which showed a significant reduction in BMI SDS, total body fat mass percentage and waist circumference SDS after a 12-week intervention programme which was sustained at 6 months. The low drop out rate of 12% in a study including adolescents is particularly encouraging(41).

The MEND programme that is another family based community intervention has been completed by at least 25,000 children (between 7-13 years) in the UK. The randomised control trial evaluating the effectiveness of the Mind, Exercise, Nutrition, Do It Programme also showed a significant reduction in the waist circumference and BMI (-4. 1 cm and -1. 2 kg/m2) on comparing the intervention and control group as well as benefits in cardiovascular fitness, physical activity levels and self esteem(42).

Whitlock et al in 2008 (43) evaluated a total of 18 behavioral intervention trials including 1794 obese children and adolescents aged 5-18 years. The results showed that the amount of relative or absolute weight change associated with these programmes in school or specialty health care setting is generally modest (BMI difference of 1. 22 kg/m2 (0. 75, 1. 69) and evidence to suggest that these changes could be sustained over 12 months after the end of treatment was very limited. Long-term weight control is more likely to be successful in patients who are highly motivated and engage in high levels of exercise (approximately 1 hour/day), eat a low calorie, low-fat diet, eat breakfast regularly, monitor their weight regularly and maintain a consistent pattern of eating during weekdays and weekends(44).

The Cochrane review of lifestyle interventions to treat paediatric obesity which included 54 randomized controlled trials of which 12 focused on physical activity, 6 on diet change and the remaining 36 on behavioural management(45) showed that there was very little to recommend one treatment over the other with the best results seen with combined behavioural interventions.

Weight loss camps and residential programmes for obese children and young people have been around for over 50 years. In a 2011 systematic review of 22 studies which included at least 10 nights in camp, substantial weight loss was seen in all the studies.

Comparing this with out patient management, attrition rates were lower and there was a 191 percent greater reduction in percent overweight post the camp and 130 percent greater reduction at follow up. Those programmes that had a cognitive behavorial therapy (CBT) component alongside the controlled diet, activities and nutrition education did substantially better in keeping the weight off at follow up.(46)

More recently in a study examining treatment outcomes and medication rates in almost 650 obese adolescents who attended 10 different CBT immersion camps in America and the UK showed that prescription rates for psychotropic medication were ten times higher in the USA when compared to the UK. Engagement and weight loss were similar in both the medicated and non-medicated groups. The medication group reported more distress both initially and at the end of the study, though the mood of both groups improved after camp attendance(47).

There are very few studies focussing on children and adolescents with severe obesity. STOMP, an intensive family focussed behavioural support programme offered over 2 years (mean BMI Z score >3) showed no change in BMI Z score though QoL and depression improved. (48). Another study reviewed the efficacy and safety of high protein low carbohydrate diets versus low fat diets in severely obese adolescents. Both groups were encouraged to do 30 minutes of exercise each day. Seventy percent percent of the young people completed the intervention with both groups showing a significant change in BMI but this was greater in the low carbohydrate diet group though there was no difference between the two groups at longer term follow up. There were no serious side effects noted(49)

**Low calorie diets**

A relatively old study that included a very low calorie diet followed by a hypocaloric diet accompanied by behaviour and exercise modification in 56 overweight children aged between 7-17 years showed a significant decrease in body weight and body fat at the end of one year. Adherence was good with 93 percent completing the acute phase of 10-20 weeks and 63 % completing the one year programme(50)

A number of studies have shown an improvement in glycemic control and reversal of type 2 diabetes after bariatric surgery even before substantial weight loss has occurred. In an adult study comparing the effects of Roux en gastric bypass surgery and very low calorie diets (500 kcal) for 3 weeks, similar weight loss as well as improvement in insulin sensitivity, beta cell function and acute insulin secretion were seen in both groups(51)

Recent adult work has shown remission of type 2 diabetes in 46 % of patients who took part in a cluster randomized trial of a low energy diet (LED) in primary care (DiRECT study) compared with conventional care and lost an average of between 10-15 kg. (52)

A small pilot of 8 young people with type 2 diabetes in Australia (the SHAKE –IT study) showed that just over half could adhere to the diet for 8 weeks and off these, 4 were clinically in remission at 34 weeks suggesting that a low energy diet may be a feasible option for young people with severe obesity. (53). An older retrospective study of 20 young people on a ketogenic, very low energy diet (<800 kcal versus LED which is >800 kcal) showed similar results (54) and although adherence is difficult, recent adult work and the pilot from Australia make the LED a potential alternative.

#### Drugs

In children, NICE does not generally recommend pharmacotherapy except in certain specific situations. These include life-threatening co-morbidities such as raised intracranial pressure or sleep apnoea in children under 12 and physical or significant psychosocial co-morbidities in children twelve years or older(10).

The Scottish Guidelines take a slightly different approach advocating the considering of medication if BMI is greater than the 99. 6th centile with co-morbidities (their definition of severe obesity) or in very severe or extreme obesity(11).

A systematic review and meta-analysis of randomised trials on the non-surgical treatment of paediatric obesity was published by the US Endocrine Society in 2008(55). Meta-analysis of pharmacological interventions included nine trials that concluded that short-term medication was effective with sibutramine resulting in a BMI loss of 2. 4 kg/m2 (CI 1. 8-3. 1) while with orlistat the change was of 0. 7 kg/m2 (CI 0. 3-1. 2).

**Sibutramine** – an inhibitor of noradrenaline, serotonin, and dopamine reuptake- was removed from the UK market in 2010(56) following reports of increased cardiovascular adverse events (elevated blood pressure, pulse rate, non-fatal heart attacks and strokes) in adult patients treated with the drug in the SCOUT study(57).

**Orlistat** - a lipase inhibitor, which inhibits the absorption of dietary fats, is still prescribed in the UK. In a randomised control pilot trial, the orlistat and control group were given a diet plan and asked to increase physical by 30 minutes a day. BMI decreased significantly in the orlistat group (4. 09±2. 9 kg/m2) while it increased by 0. 11±2. 49 in the control group. However, compliance is generally poor, with reports of anything between 30-90% of patients opting to stop treatment within a few months (58, 59). This poor compliance is due mainly to the gastrointestinal side effects of the drug, which most young people and their families find unacceptable. These include fatty/oily stool, oily spotting, increased frequency of defecation, abdominal cramps and pain (45). Mcduffie’s study in 20 obese white and African American adolescents with a mean BMI of 44. 1 kg/m2 was more promising with significant decreases in weight and BMI and 80 percent of prescribed medication reported as being taken(48).

**Metformin** - (an oral biguanide) is not currently licenced for use in treating obesity in children. During a double blind randomised control trial in 28 severely obese adolescents with normal glucose tolerance (mean BMI 40. 3±5. 7 kg/m2), the metformin group lost weight and subcutaneous fat and showed a 35 percent improvement in insulin sensitivity(60). The MOCA study, a multi-centre randomised placebo controlled trial of metformin in obese children and young people aged between 8-18 years with insulin resistance and/or impaired glucose intolerance has shown that metformin is associated with a significant reduction in BMI SDS at 6 months when compared with placebo. There was also a beneficial treatment effect on fasting glucose, liver enzymes and adiponectin/leptin ratio(61). The Viner systematic review of 320 patients showed a reduction in BMI of1.42 kg/m2 (0.83-2.02) and HOMA-IR score of 2.01% (0.75-3.26) when compared to placebo. These studies will help add to the armamentarium we should offer our patients.

**Topiramate** has been used for seizure control for many years, and can help with weight loss by controlling cravings. In a retrospective review of 28 patients with a mean age of 15.2 years (±2.5), and baseline BMI of 46.2 kg/m2 (±10.3), an almost 5 percent drop in BMI was seen at 6 months.(62) Topiramate is not currently licensed for weight loss in children and young people and randomized control trials are needed to establish safety and efficacy. Side effects include confusion and paraesthesis of arms and legs.(63)

**Phentermine** is a widely prescribed anti obesity medication in adults. A study comparing

phentermine with lifestyle modification advice versus life style change alone showed a 4 percent decline in the group that had phentermine included. An increased heart rate was seen in this group but there was no change in blood pressure.(64).

It is approved in America for young people over 16 years but not worldwide.

**Liraglutide**- a glucagon like peptide 1 receptor agonist has recently been made available on the NHS for weight management in adults. In a review of the current phase III trials (5 RCT), a 4-6 kg weight loss was seen with liraglutide with a significant number of patients showing between 5-10 percent weight loss. Gastrointestinal side effects which usually occurred when treatment was first commenced, its cost and the fact that this is given by injection were quoted as barriers to its acceptability(65).

This has not yet been licensed in children and young people for weight management, though its efficacy and safety in overweight young people with type 2 diabetes has been established with a 1.3 % drop in HBA1c at 1 year in the liraglutide group when compared with the placebo group(66). This is now being used in T2DM in young people following the recommendation by the European Medicines Agency.(67)

**Newer research**

There are 2 types of adipose tissue - white fat and brown fat. Brown fat stores lower levels of fat and contains many mitochondria and lipid droplets and can be activated to oxidise fatty acids and thus control obesity by using the excess fat for heat production. This is possible due to the presence of uncoupling protein 1 (UCP 1) on the inner mitochondrial membrane of brown adipocytes where it uncouples the respiratory chain from ATP generation. White adipose tissue has been shown to be extremely plastic with beta adrenergic stimuli and cold exposure resulting in an increase of brown adipocyte like cells, also called beige or ‘brown in white’ or brite cells. These cells are shown to be similar to brown adipocytes and may have similar heat production ability. Phytochemicals (such as flavonoid curcumin found in turmeric, fucoxanthin from algae and dietary capsaicin), myokines, hormones like norepinephrine, and pharmaceutical agents like adrenergic agonists) are known modulators of browning. (68)

Some more experimental work including looking at already licensed drugs (such as exenatide and sildanefil) that induce browning of white adipose tissue is underway but the feasibility of this in humans is unproven. (69)

#### Bariatric Surgery

Bariatric surgery is effective in leading to significant and sustained weight loss in adult and populations with improvement in co-morbidities(70). A systematic review and meta-analysis of bariatric surgery for paediatric obesity (641 young people, 19 studies, average age 16. 8 years, average BMI 48. 8 kg/m2) showed significant decreases in BMI in both the gastric band and bypass group (-13. 7 to -10. 6 kg/m2 in the banding group and -22. 3 to -17. 8 kg/m2 in the bypass group). More importantly, though co-morbidity resolution was sparsely reported, surgery did seem to lead to resolution of diabetes, hypertension, sleep apnoea and dyslipidemia(71).

There is only one randomised control trial (72) in adolescents comparing gastric banding with an optimal life style program (25 in each arm) from Melbourne, Australia with 2 year follow up (42 completed the study). Main outcome was weight loss but secondary outcomes such as impact on quality of life, and comorbidities such as insulin resistance and metabolic syndrome were also considered. Mean weight loss in the intervention group was 34. 6 kg (95% CI, 30. 2-39. 0), change in BMI was 12. 7 (95% CI, 11. 3-14. 2) and drop in BMI z score of 1. 07 all of which were significant when compared to the lifestyle group.

Thirty three percent of the young people had to go in for a further procedure following the initial band fitting. Overall, the gastric band achieved a greater percentage of weight loss when compared to life style management and led to improved quality of life and reversal of metabolic syndrome.

Recently, the Teen-LABS consortium reported the initial outcomes of 242 adolescents who underwent weight loss surgery at 5 US centres (161 by pass and 67 sleeve gastrectomy). At 3 years after the procedure, meant weight loss was 27 percent, with remission of type 2 diabetes in 95 percent (19/20-data not available for a further nine), remission of high blood pressure in three quarters (96 participants at baseline) and dyslipidemia (171 baseline) in 2/3 with significant improvement in weight related Qol. However, there were significant side effects.

At baseline, only 5 % had low ferritin levels, but at 3 years over half had low iron stores. Vitamin B12 levels also reduced by 35% in the 3 years and 8% had a deficiency at 3 years. Thirty young people (13 percent) had to undergo one or more additional procedures (total 47 intra-abdominal procedures) of which only three were unrelated to the bariatric procedure. There was one death 3.3 years the gastric bypass related to hypoglycemia. (73)

NICE guidance suggests that bariatric surgery may be appropriate for children in exceptional circumstances.(74)

Figure 4 - NICE criteria for bariatric surgery in adolescence

Surgery is not generally recommended for children or young people. Consider surgery for

young people only in exceptional circumstances, and if:

However, there is a marked reluctance by paediatricians and commissioners to consider this. This partly stems from the worry about informed consent from minors, timing of the intervention and whether appropriate systems are in place to address the unique developmental and psychological needs of young people(75).

The implications of performing an irreversible procedure in a young person also need to be considered.

In summary, bariatric surgery in severely obese adolescents is effective, however is reserved only for those who meet certain criteria(76). Currently, bariatric surgery for adolescents is nationally commissioned by NHS England for which here is specific patient pathway and service specification.

At Sheffield Children’s Hospital, one of only 3 centres in the UK offering these quaternary services for extreme childhood obesity, referrals for bariatric surgery for young people are considered on a case by case basis weighing the potential benefits and harm for each young person (77).

It is increasingly clear that there is a gap to meet the needs of severely obese young people. Lifestyle intervention and medication are of minimal benefit. Bariatric surgery while efficacious still raises concerns due to the concerns about complications, limited long term data and the permanency of the procedure.

The aim of this thesis is to explore the use of intra-gastric balloons as a potential reversible intervention for adolescent obesity as this may be considered more acceptable for young people. The rationale for the use of the intra-gastric balloon, evidence basis and its efficacy and safety are discussed in the next chapter of the thesis.

We therefore proposed a feasibility study looking at the effectiveness of intra-gastric balloons (IGB) supported by a lifestyle intervention programme to aid weight loss in severely obese adolescents (>3. 5 SDS). These young people would be eligible for bariatric surgery and meet the exceptionality criteria of the NICE guidance, which has been previously outlined.

The aim was to utilise the short term weight loss associated with intragastric balloons supported by a behaviour management programme based on a previously trialled local programme (25) and bring about sustainable weight loss by facilitating longer term behavioural change. It used the Tran theoretical model as the guiding framework with cognitively based intervention strategies such as consciousness raising and cognitive reappraisal in the early phases and behavioural based interventions in later blocks.

## Intra-Gastric Balloon

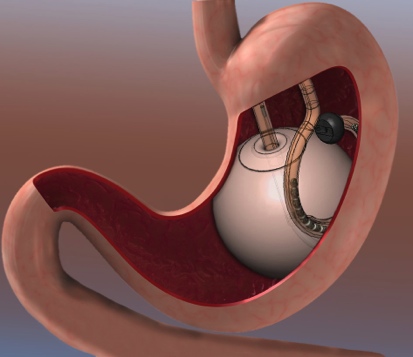
### History

Intra-gastric balloons were first proposed as an adjunct to weight loss almost 30 years ago (78) but some of the earlier models suffered from technical (like early deflation) and placement problems, were ineffective and hence abandoned. An expert committee meeting was held in 1987 to define what an ‘ideal’ balloon should be and how a weight loss programme based on these should be organised (79). Following this consensus meeting, 3 models of intra-gastric balloons are now commercially available. The first one called the BIB -Bioenterics intragastric balloon is filled with saline and has now been used in thousands of patients and was the balloon we used in our study. There were also 2 other air filled models, the Heliosphere Bag and the Endogastt. The Heliosphere is a double bagged polymer balloon covered with silicone which is filled with air again to a final volume of 650 to 750 ml. Though, there is some evidence about its effect on weight loss, it is plagued by system failures such as partially deflated bags and in another the bag could not be found. (80). However, later studies have been more promising with a 32 patient study showing a mean weight loss of 13.6 kg of which 9.8 kg was maintained at 18 months. (81) The Endogastt is an air filled adjustable balloon which is permanently placed in the gastric fundus and has been shown to bring about clinically significant weight loss in obese adults, but is less commonly used now except in cases of the morbidly obese(82). Subcutaneous infections were seen in 12 percent and port erosions in 5 percent in a study of 59 patients with an excess weight loss of 39.2 % (20 patients).

The BIB is sited endoscopically and can remain within the stomach for approximately 6 months because beyond this period, the risk of spontaneous deflation increases significantly (83). The balloon is inflated and placed in the body of the stomach. It presence reduces the capacity of the stomach and reportedly enhances feelings of satiety. The balloon is thought to be effective by filling up the stomach (84). The balloon is deflated 6 months later and again removed endoscopically.

Balloons are less invasive and safer than bariatric surgery, are temporary (stay in for 6 months) and hence could be more acceptable alternative for young people. Whilst there is evidence as to their efficacy in promoting short term weight loss (83), one of the key questions that remains is whether individuals regain weight lost when the balloon is removed.

Figure 5- Intragastric Balloon



reference: PRweb. com/StomachSpatz-FIGa system

### Bioenterics intragastric balloon-current evidence for weight loss

Dumonceau recently reviewed the literature focussing only on the BIB intragastric balloon. The review included 30 studies which included a total of 4877 adult patients(83). Some of the studies reported absolute weight loss, others reported change in percentage overweight and others reported change in BMI. Some studies considered only morbidly obese individuals (BMI > 40), others included individuals with lesser degrees of overweight. Of the studies included in the review 18 were prospective (but only five were randomised) and 12 were retrospective studies. The average weight loss reported across the non-randomized studies was 17. 8 kg with the average weight loss ranging from 4. 9 kg to 28. 5 kg in specific studies. The average reduction in BMI was 4. 0 - 9. 0 kg/m2. As expected, absolute weight loss was highest in those whose weight and BMI was highest at entry into studies (BMI >40) but if one considered the percentage of excess weight lost this tended to be higher in individuals with more moderate obesity (BMI less than 40 kg/m2) and those who did not have eating disorders.

The review could consider severe complications only from 20 of the 30 studies (as reporting of complications was very variable across the whole group). Severe problems were not common with a 0. 21 % and 0. 17% incidence of perforation and intestinal obstruction respectively. These were seen mostly in patients who had had previous bowel surgery. Early balloon removal due to intolerance was seen in 2. 4% patients and 3 deaths (2 with gastric perforation and 1 with bronchoaspiration following BIB insertion) were reported giving a treatment related death rate of 0. 07%, which compares favourably with the rate of 0. 5 % quoted for bariatric surgery(85).

A separate meta-analysis by Imaz (86) studying the efficacy of the Bioenterics Intragastric Balloon included pooled data from 15 articles (3608 patients). Sixteen studies were selected of which 14 were case series and two were RCT’s. The criteria included for evaluation for case series included consecutive cases, explicit inclusion criteria and drop out rate <20%, all of which were met by 65% of the studies. Based on this meta-analysis, at balloon removal, the average weight loss was 14. 7 kg or 12. 2% of initial body weight, which represented a loss of 32. 1% of excess weight and a change in BMI of 5. 7 kg/m2. A beneficial health effect as well as improvement in mortality rates is seen with total body weight loss of 10 %(87). It was unclear how the percentage of excess weight was calculated in the meta-analysis, though the standard recommended by Dietel is fairly simple and widely used(88). The conclusion from the meta-analysis was that the BIB was an effective short-term treatment to promote weight loss within a multidisciplinary team but there was no data to comment on its longer-term efficacy.

The review also considered the safety of the BIB. Early balloon removal was required in 4. 2% of patients due to reasons of abdominal pain, obstruction, and deflation with and without displacement of the balloon, perforation, dehydration and gastric ulcers.

Minor side-effects were relatively common with 8. 6% of patients experiencing some nausea and vomiting and 5% complaining of abdominal discomfort, particularly early after balloon insertion. Serious complications such as intestinal obstruction occurred in 0. 8% of patients (26 patients) and gastric perforations occurred in four patients (0. 1%) of whom two patients subsequently died. Both had had previous gastric surgery (Nissen fundoplication).

Whilst the more recent evidence based review by Dumonceau and the meta-analysis by Imaz suggest that the BIB is effective, the Cochrane review by Fernandaz in 2007 concluded that intragastric balloons did not show significantly greater weight loss than conventional treatments (defined as intensive dietary support programs)(89) . The emphasis within the Cochrane review was on the quality of studies and only nine published studies with 395 patients were included. Six of the nine studies had follow up for less than one year and only one study included a twenty-four month follow up. The two studies with maximum number of patients used the two balloons that have now been withdrawn. (Garren Edwards balloon and the Dow Corning balloon respectively) (90), (91). The conclusion from the review was that the intra-gastric balloon was generally safe and that evidence available to recommend this treatment was limited because of the large clinical and methodological variation in the trials that were reported(89).

### Effect of intra-gastric balloon therapy on QOL in adults

Only one study (119 patients, 86 female, mean age 37. 8 years), conducted in Hong Kong assessed the impact of intra-gastric balloon treatment on quality of life using a validated assessment tool, the Chinese version of the SF -36 (92). Only the short-term impact before and immediately after treatment was examined and found that physical and social functioning, general health and vitality were all improved. There was no longer-term follow-up to assess whether improvements in quality of life was maintained.

### Effect of intra-gastric balloon therapy on co-morbidities

It is well known that even modest decreases in weight lead to significant health benefits(87). More specifically, in relation to the BIB, Mui et al showed that the incidence of metabolic syndrome decreased significantly, HBA1c improved, as did cholesterol, triglycerides and blood pressure in their cohort of 119 ethnic obese adult Chinese patients treated with intra-gastric balloon therapy (92).

An Italian retrospective study of over 2500 patients (mean BMI 44 kg/m2 at study entry, mean age 38. 9 years) showed that rates of hypertension, diabetes, osteoarthropathy and obstructive sleep apnoea improved significantly with use of intra-gastric balloons in 90% of the patients at balloon removal(93). There is no data on how the co- morbidities evolved during longer term follow up or potential changes in mortality after BIB treatment. Though, some studies of the BIB do include adolescents, improvement in co-morbidities in young people have not been separately reported. We do know from other work, however that weight loss (due to public health interventions) with even modest decreases in BMI z score (≥0. 23) can lead to an improvement in cardiovascular risk factors (94) in obese adolescents.

Following bariatric surgery extremely obese diabetic adolescents experience significant weight loss and remission of type 2 diabetes mellitus (95). However, there has been no systematic prospective study to assess specifically the impact of weight loss with the intra-gastric balloon on clinical and psychological co-morbidities in children.

### Longer term studies in adults

There are very few studies looking at weight maintenance over a longer term following intragastric balloon treatment. In a randomized, double blind trial (43 patients, similar age range and weight, mean BMI 43. 3 kg/m2) of balloon or sham treatment of 3-month duration followed by balloon treatment for a further 9 months in both groups, there was no difference in the weight loss in the 2 groups on analysis at 3 months. However, average weight loss of 17% was obtained in all patients at the end of the first year of which 10% was maintained after a further balloon free year (96). Just over half the patients maintained a weight loss of greater than 10%, which is considered clinically significant at the end of the 2nd balloon free year.

In another study by Herve et al, ¾ patients had lost >20% of excess weight at the time of balloon removal but this was sustained in only just over half the patients one year later(97).

### Adolescent studies

One of the earliest studies looking at intragastric balloons in severe adolescent obesity (ages 11-17) was disappointing. This showed that while the balloons were well tolerated, only a non-significant drop in BMI was observed at 3 months (p=0.07), and this temporary benefit was not sustained with BMI at 6 months higher than at the start of the study(98).

More recently, some studies appear to have included adolescents within their cohorts but only one presented the data separately to adult data. In the trial by Sallet the mean decrease in BMI was 5. 0 kg/m2 in a subgroup of 21 adolescents compared to 5. 3 kg/m2 in 302 adults in this series. Only five adolescents had follow-up data at one year follow balloon removal but weight loss had been maintained in these individuals(84).

Another study in Greece has looked at a group of 14 older adolescents (mean age 18. 5 years) who underwent intra-gastric balloon therapy over a period of 6 months resulting in an average BMI reduction of 2. 8-kg/m2 and weight loss of 10 kilograms.

However, this group is essentially that of young adults, no lifestyle or psychological support was provided and compliance with follow up was poor with no long term data available (99).

A retrospective study of 27 adolescents (23 female, 14-19 years) with a mean BMI of 37.04(6.29) showed a better response with a mean weight loss of 15.99 kg (5.87) at balloon removal. However, there was no longer term data available(100).

Locally there was experience of one 14y individual who lost 40 Kg of weight by use of an intra-gastric balloon over a 6-month period prior to a definitive banding procedure in Sheffield(77).

Therefore, there is a clear gap in studies looking at intra-gastric balloons as a temporary intervention supported by a life style programme in severely obese adolescents and its longer term impact on weight and metabolic outcomes. There is also a need to address the concern about rapid weight loss and the impact of this on the growing skeleton.

The next chapter of the thesis outlines the metabolic changes and co-morbidities known to be associated with childhood obesity, how best to evaluate these changes following an intervention (intra-gastric balloon supported by a life style programme) and then longer term. It also discusses some more experimental data related to change in adipokines, ghrelin and incretins during an OGTT and correlations if any with changes in weight loss.

## Insulin glucose metabolism, Incretins, Adipokines and Ghrelin and changes seen in obesity and following weight loss

Obesity is the most common cause of insulin resistance in children and young people. This is also associated with dyslipidemia, type 2 diabetes and long term vascular complications.

### Insulin Glucose Metabolism Parameters

Obese children have insulin resistance (IR) alongside problems with glucose metabolism –impaired glucose tolerance or frank type 2 diabetes. The hyperinsulinemic –euglycemic clamp is the accepted gold standard to measure insulin resistance. (101) However, this test is invasive and time consuming. It is easier to use the HOMA-IR which estimates insulin resistance based on the fasting glucose and insulin measurements and has been validated in several clamp studies in non-diabetic children(102, 103).

We chose to use measures of insulin resistance rather than sensitivity as we the expected weight loss, changes in IR were far more likely than change in beta cell function.

Lee et al showed that in a population based study of about 1800 young people in the USA, HOMA-IR is significantly higher in the obese when compared to their normal weight counter parts (weight accounts for 29 percent of the variance in HOMA-IR) and that none of the other factors (such as age/sex/race) play as important a role. (104)

HOMA-IR is calculated by multiplying insulin (micro units /millilitre) and glucose (mmol/litre) and dividing this by 22. 5. (105)

A level of > 4. 4 (which is 2 sds above the mean for normal weight adolescents) with normal fasting glucose was used as a marker for insulin resistance in our study. (104)

Other means of looking at insulin glucose metabolism are fasting insulin levels, though the definition of fasting hyperinsulinaemia in children and adolescents is not established. This is also dependent on stage in puberty as puberty affects insulin resistance with peak drop in insulin sensitivity seen in Tanner stage 3 and complete recovery by end of puberty. All the young people in our study were Tanner stage 4 or above which was one of the inclusion criteria.

Criteria for defining fasting hyperinsulinemia was based on the Lee study mentioned above (Defined as >180 pmol/l at Tanner stage 4 and >120 pmol/l at Tanner stage 5). These were modified as based on the OSCA review(12).

There is no clear definition of hyperinsulinaemia in response to glucose challenge. We have used peak insulin ≥100mU/L (600pmol/L) as a marker of OGTT hyperinsulinism based on the OSCA review.

#### Insulin area under the curve

Using area under the curve (AUC) may be more sensitive than looking at fasting measures of insulin/glucose metabolism alone. It is quite established in diabetes research with several different ways of doing it with the trapezoid method being one of the most popular due to its simplicity of using a sum of all the readings obtained at equal intervals(106).

Studies show that how the AUC is calculated can influence whether the intervention being used is considered effective or not. (107) In a study looking at OGTT before and after exercise as an intervention in obese adults, incremental, positive incremental and total AUC methods were used and showed that total AUC decreased in the intervention group but no changes were seen in the other 2 methods.

The AUC remains a recognised way of looking at the spectrum of impaired glucose tolerance/ prediabetes to diabetes in obese children and adolescents.

We used Glucose AUC, Insulin AUC as well as the AUC for the 2 main incretins GLP-1 and GIP described in detail below in our study.

### Incretins

An oral glucose load produces a much greater response in insulin secretion compared to if the same load is given as intravenous glucose; this is now known to be due to the incretins released after ingestion of nutrients from the gut which stimulate insulin secretion from the beta cells and is called the incretin effect. The 2 main incretins are Glucagon like peptide -1 (GLP-1) and Glucose dependent insulinotropic polypeptide (GIP). (108)

Both are secreted quite quickly after eating and act on the beta cells of the pancreas on different receptors which leads to glucose dependent insulin secretion. They also have a non-insulinotrophic actions such as beta cell proliferation and resistance to apoptosis.

#### GLP-1 and GIP

Glucagon like peptide-1 is a 31 amino acid hormone that is made from pro glucagon. It works by binding to its receptor (which is a part of the G protein coupled receptor family) and directly acts on the pancreatic islet cells. It also binds receptors in the hypothalamus (arcuate and dorsomedial nuclei) and the brain stem. It has 2 major molecular forms, the GLP-17-36 amide and GLP-17-37 amide. (108, 109)

It is secreted from the lower intestinal endocrine L cells in response to food and lowers blood glucose by stimulating insulin production, delaying gastric emptying and suppressing glucagon secretion(110). Due to the receptors in the brain, it also has a role in reducing intake and bringing about increased satiety. Its secretion is usually biphasic with an early phase within 10-15 minutes followed by a later phase which is longer and lasts 30-60 minutes. As the location of the L cells is quite distal, a number of indirect mechanisms are likely to come into play to account for the early GLP-1 response including the autonomic nervous system and neurotransmitters GRP, Acetylcholine and GIP (108). GLP-1 also promotes satiety and receptor activation results in weight loss. Meals high in fats and carbohydrates are the main physiological stimuli for GLP-1 secretion.

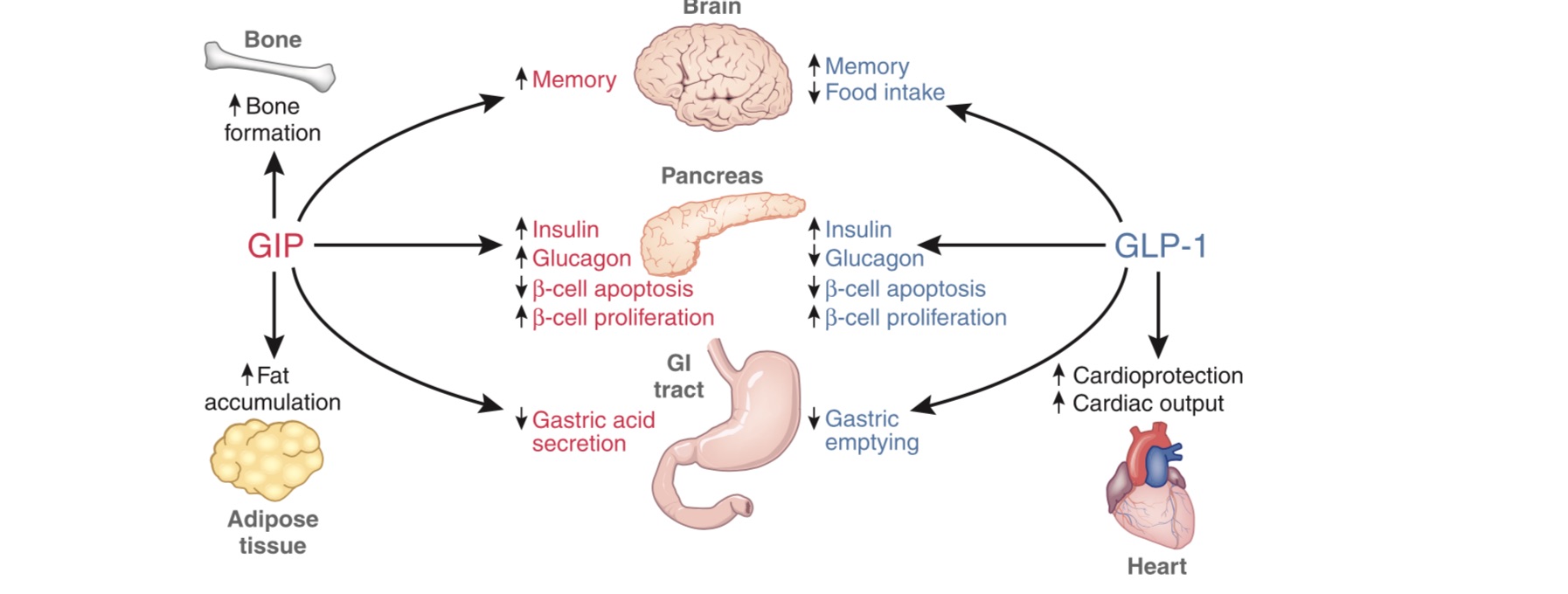
Glucose dependent insulinotropic polypeptide or GIP (as it is now called) is the first known incretin and was originally isolated from porcine intestine. It was noted that it could inhibit gastric acid secretion, hence the name Gastric Inhibitory peptide. It is a 42-amino acid hormone and is secreted from the k cells of the upper small intestine. It was later shown to independently stimulate insulin secretion in healthy volunteers by acting on pancreatic islets directly. It is the rate at which nutrients are absorbed that prompts GIP release rather than just their presence in the small intestine.

The GIP Receptor (GIPR) is like the GLP-1R and belongs to the 7-transmembrane –spanning heterotrimeric G protein coupled receptor superfamily.

In healthy subjects, upto 60 percent of the insulin secretion seen after glucose intake is thought to be due to GLP-1 and GIP.

Figure 6 below from the Seino review shows the pancreatic and exopancreatic function of both glucose-dependent insulinotropic polypepide (GIP) and glucagon-like peptide (GLP)-1.

Figure 6 - GLP-1 and GIP Action

 Ref (109)

Plasma levels of total GLP-1 at fasting are 10-20 picoMoles in healthy Caucasians reaching 30-60 after 30 min of a 75-gm glucose load or a mixed meal. (111). The peak level reached can depend on the size and the composition of the meal.

Baseline levels of total GIP are 5-20 pM and reach levels of 50-100 at 30 minutes after a glucose load but increase still further to 100-150 pM after 60 minutes following a mixed meal suggesting that meal content also plays a role in the response.

In a study looking at this with Japanese subjects, it was found that the baseline GLP-1 levels were lower and while similar increases as in the Caucasian population were seen with glucose, the increase after the meal was negligible. This could account for the reduced secretion of insulin seen in Asians and the development of diabetes at a lower BMI. For GIP, total values were higher in Japanese subjects but intact values were the same in both ethnic groups, implying that how these are processed may be different (112).

They both undergo degradation catalysed by DPP-4 (dipeptidyl peptidase) which is a serine protease that cleaves dipeptides from the amino terminus of a protein containing alanine or proline residue in position 2 and this changes their activity. Both total and intact forms must be measured ideally. The half lives for intact GIP and GLP-1 are approximately 5-7 minutes and 2 minutes respectively. GLP-1 is eliminated through the kidney involving both tubular uptake and glomerular filtration.

Recent studies comparing GLP-1 release in diabetics and healthy controls have shown that GLP-1 concentrations are slightly reduced in participants with impaired glucose tolerance and more significantly reduced in T2DM representing a continuum of sorts(113).

As the elimination rates of GLP-1 are the same in normal weight, obese and patients with type 2 diabetes, the reduced levels are thought to be due to decreased GLP-1 secretion. Some studies also report that the decreased incretin secretion seen in type 2 diabetes in Caucasians is not seen in some other ethnicities (Japanese/Korean)(111).

Studies suggest that fasting and post prandial circulating GLP-1 levels are increased after procedures such as the bypass and sleeve gastrectomy but that there is either no change or a reduction in levels following purely restrictive procedures such as the bypass. (114).

In some studies, a reversal in type 2 diabetes has been shown after gastric bypass even before the weight loss and is postulated to be due to the increased incretin effect(115).

Most of the current work on incretins has adult subjects and there is very little information about incretins in young people including those newly diagnosed with type 2 diabetes.

Park et al looked (2015) at incretin levels in obese Korean adolescents with newly diagnosed diabetes and age and sex matched controls without diabetes. The mean age was 13.8± 2 years and mean BMI Z score was 2.1±0.5. They showed that during an OGTT, the total GLP-1 secretion was higher in the group with type 2 diabetes (116). This finding which is contrary to other studies maybe since this cohort was younger with a short duration of diabetes.

Obese children seem to have reduced GLP-1 levels with varying changes reported after weight loss (117). In a study looking at the impact of a life style intervention programme (with exercise, nutrition support and psychological therapy as key components) to bring about weight loss, there was no difference in the GLP-1 levels between obese and lean young people at baseline. However, on multiple linear regression analysis, the GLP-1 was significantly correlated with the insulin (p=0.028) and HOMA (p=0.019). There was a significant reduction in the GLP-1 in the obese cohort after weight loss which again correlated with change in insulin (r=0.46 ,p=0.001) and HOMA (r=0.28, p=0.036) but not with glucose, BMI or percentage body fat(118).

GIP levels are normal or thought to be slightly elevated in patients with type 2 diabetes. Like GLP-1, the kidneys are again the main route of clearance of GIP.

GIP levels are also known to be high in obesity and have a role in fat storage with direct action on adipose tissue. GIP effects include stimulating fatty acid synthesis and re-esterification, incorporation of fatty acids in triglycerides, up regulating lipoprotein lipase activity and reducing the lipolysis due to glucagon. However, it also has the opposite effect with GIPR-/- mice showing reduced adipocytes and no obesity even after being given a high fat diet for several months(119).

**Effect on bone**

Membrane receptors for GIP are present on osteoblasts, osteocytes as well as osteoclasts and when GIP is given, both levels of collagen type 1 messenger RNA and alkaline phosphatase increase suggesting an anabolic effect on bone.

.(120) There is evidence to show that GIP inhibits bone resorption in vitro in an organ culture system and has a role to play in the reduced resorption seen after eating.(121)

GIP levels have been found to be reduced both before and after food after bypass procedures though the effects post bariatric surgery still remain unclear.(122)

GLP-1 administration in type 2 diabetic, insulin resistant and normal mice has been shown to improve trabecular parameters in those with both T2DM and IR suggesting that GLP-1 could improve bone formation and structure related to glucose tolerance.(123)

The impact of the potential increased GLP-1 levels seen after some forms of bariatric surgery in humans is still unclear.

We sought to measure the baseline, 30, 60,90 and 120 minute GLP-1 and GIP levels in the severely obese young people following ingestion of a 75-gm glucose load and to compare this at all 3 points-pre-balloon insertion, post balloon removal and 18 months later.

### Adipokines

#### Leptin

Adipose tissue is important for both energy storage but also releases a large number of proteins, called adipokines. These include leptin, adiponectin, visfastin and resistin which not only regulate fat metabolism, have a role in illnesses associated with obesity but also have a role in bone physiology.

Leptin is a 167 amino acid and was discovered almost 25 years ago in 1994(124). The ob gene located on chromosome 7q31 produces leptin which has a role in energy balance, suppressing food intake and bringing about weight loss. When a biologically active purified form of recombinant mouse OB protein was given, it reduced amount of food eaten and weight in ob/ob and diet induced obese mice but not in db/db obese mice(125) Leptin acts via the arcuate and ventromedial nucleus in the hypothalamus to suppress appetite and is reduced in periods of fasting to increase the appetite. (126)

The leptin receptor is a single –transmembrane domain receptor of the cytokine receptor family (Ob-Rb) and works by activating the Janukinase2 in the signal transduction pathway. There is also a soluble leptin receptor (sOB-R), the levels of which are lower in obesity thus leaving increased amounts of free leptin circulating in the system.(127)

Leptin levels vary through the day with peak levels overnight and a drop at midday. (128). Therefore, time of sampling is important which was adhered to in this study.

In a study looking at leptin levels in serum and CSF in lean and obese individuals, the serum leptin levels were ten-fold higher in the obese population than in the CSF suggesting impaired leptin transport in obesity. (129)

Though intuitively it may seem that increased leptin in obese people would result in decreased appetite and then reduced food intake, this does not happen as increased fat mass leads to leptin resistance and decreased leptin signalling in the brain which disrupts the satiety response.

True leptin deficiency in obese individuals is very rare and is due to a homozygous ob gene mutation and is the only condition where leptin therapy is beneficial.

Leptin secretion is primarily dependent on fat mass with increase in circulating levels with increased fat mass (130)and decreased serum concentration following weight loss with the changes correlating with change in fat mass, serum insulin and insulin resistance index(131).

Some studies suggest that this reduction in leptin could be associated with the bone catabolism seen after bariatric surgery. In a prospective study of 20 adults who underwent Roux- en-Y Gastric Bypass (RYGB) , increased serum N Telopeptide of collagen (NTX) at 6 and 18 months correlated with the decrease in serum leptin levels, an association that persisted in multiple regression analysis. (132).

**Effect on bone**

Bone cells, the osteoblasts or bone forming cells and osteoclasts, the bone resorption cells also secrete proteins called osteokines that influence bone metabolism and are influenced by changes in adipokines (133).

Leptin is now emerging as a regulator of bone mass by direct anabolic effect on bone cells in several different ways.

1. Leptin deficient *ob/ob* mice when given subcutaneous leptin showed an increase in femoral length, total body bone area , bone mineral content and bone density due to increase in both cortical and trabecular bone(134).
2. Leptin also promotes human osteoblastic mineralization and acts as a growth factor for chondrocytes increasing the width of the chondroprogenitor zone in a dose dependent manner. (135)
3. Bone marrow adipocytes in humans can also produce leptin. In a primary culture of fetal calf and horse sera, cells containing vesicles and lipid droplets were seen within 15 days, suggesting that while extramedullary adipose tissue and BM adipoctyes may have different effectors, they can be a source of leptin.(136)
4. Leptin and its receptor are also expressed by normal human osteoblasts. Prolonged exposure of iliac crest osteoblasts to leptin resulted in collagen synthesis, cell differentiation, in vitro mineralization, cell survival and possible osteoblastic signaling.(137)
5. Leptin administration can also prevent bone loss associated with disuse in tail suspended female rats by both inhibiting bone resorption but also preventing the decrease in bone formation.(138)

In contrast, several studies have shown an indirect antioestogenic effects via the hypothalamus on trabecular bone.

1. This was first reported in leptin deficient and leptin receptor deficient mice who showed increased trabecular bone mass independent of body fat with reduction in bone mass following leptin administration. (139)
2. Leptin appears to exert this this anti oestogenic effect on the ventral hypothalamus through stimulation of Y2 receptors and possibly Y4 receptors in the arcuate nucleus, as both Y2 receptor deficient mice or those with selective deletion of hypothalamic Y2 receptors in mature Y2 knock out mice result in an equal increase of trabecular volume in 5 weeks. (140)
3. Analysis of Adrb-2 deficient mice shows that bone resorption is favoured by the sympathetic nervous pathway by increasing the expression of Rankl which increases osteoclastogenesis and reduces bone formation. (141)
4. However, osteoclastic bone resorption can be reduced through an alternative pathway at the level of the hypothalamus through induction of Cocaine and Amphetamine Regulated Transcript (CART) expression (which is controlled by leptin), resulting in an inhibition of RANK-L production by osteoblasts. (141)

Thus, the mechanism of action of leptin on bone is multifold.

Congenital leptin deficiency or leptin receptor deficiency result in extremely severe early onset obesity with T cell immune deficiency and other endocrine abnormalities such as hyperinsulinism, and hypothalamic hypogonadism. All the 3 children reported by Farooqi and their group showed that they had normal whole body bone mineral content and density despite no detectable leptin (142). When treated with subcutaneous daily injections of recombinant leptin for 4 years, improvement was seen in fat mass, hyperinsulinemia and appetite and through normalization of thyroid hormone levels, also facilitated normal pubertal development. (143)

We would expect that obese adolescents would have a reduction in leptin levels as seen consistently after weight loss. This would lead to a reduced direct effect of leptin on bone cells and potentially lower cortical bone mass and increased trabecular mass. However, effects of leptin can also be age dependent as the skeleton matures.

We measured fasting leptin levels at all the 3 time points; baseline before balloon insertion, 6 months at balloon removal and 18 months later.

#### Adiponectin

Adiponectin is opposite to leptin in that its circulating levels are reduced in obesity, insulin resistance and type 2 diabetes(144) independent of adiposity.

Adiponectin levels range from 0. 5-30 microgram/ml in adults. Its production is regulated by the peroxisomal proliferator – activated receptor (PPAR)y which is a nuclear receptor present in muscle, liver and hypothalamus. It has anti-inflammatory effects and is protective against development of type 2 diabetes and heart disease.

In the Obeldicks programme described above looking at changes in gastrointestinal and adipose tissue peptides one year after weight loss due to a life style intervention, adiponectin levels significantly increased and (117) insulin resistance significantly improved with weight loss.

Jeffery et al reviewed the literature looking at adiponectin from infancy to adolescence and found that even in obese pre-pubertal younger children, adiponectin levels are lower compared to their normal weight peers. In older children, they found that adiponectin is associated with insulin resistance even when not taking obesity into account as well as beta cell dysfunction and some elements of the metabolic syndrome. (145).

Adiponectin seems to have a primarily negative effect on bone formation by increasing the formation of bone resorbing osteoclasts and inhibiting the production of osteoprotegerin (OPG) from the osteoblasts(146) .

A recent prospective study showed significantly increased levels of adiponectin which correlated with change in BMI a year after gastric bypass surgery(147). Therefore, potential increases in adiponectin following weight loss would further increase the adverse effects it has on bone formation.

We measured fasting adiponectin levels at all the 3 time points; baseline before balloon insertion, 6 months at balloon removal and 18 months later.

### Ghrelin

Ghrelin is a 28 amino acid peptide produced in the gastric antrum and fundus (less so in the duodenum) and is the only known circulating appetite stimulant(148). It is most active in its acylated form which is an appetite stimulant and higher levels are found proportionately in obesity though overall both fasting and post prandial levels are lower.

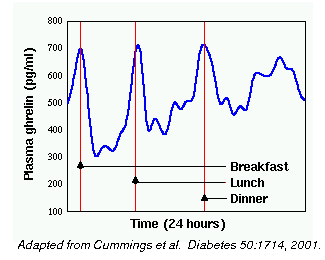
Ghrelin concentrations tend to increase pre meals and during a period of fasting, and fall rapidly after eating(149) (as depicted in the figure 7).

Studies have shown that this postprandial ghrelin inhibition may be missing in obesity contributing to the continued desire to eat(150). The impact of different bariatric procedures seems to vary depending on the type of procedure which probably depends on the amount of contact between nutrients and the gastric fundus mucosa where ghrelin is secreted(151).

Thus there maybe no changes or increased levels after restrictive procedures like the intra-gastric balloon and banding, and reduced levels after LSG and RYGB(114). In a study by Dirkson et al where 33 patients were followed up for a year after RYGB, it was noted that the ones who lost the most amount of weight had suppressed their ghrelin levels much more than the ones who responded poorly.

In obese children, ghrelin levels increased significantly after 3 months of successful weight reduction on a calorie restricted diet (152)while in another study looking at a one-year lifestyle intervention programme, there was no difference in ghrelin levels before and after(117).

Figure 7 - Ghrelin Levels with meals



Generally, banding procedures and conservative diet induced weight loss seem to result in increased levels of ghrelin while those such as the bypass suppress the ghrelin levels significantly.

We measured fasting ghrelin levels at all the 3 time points; baseline before balloon insertion, 6 months at balloon removal and 18 months later to see changes (if any ) following weight loss and to find out if these changes persisted at 18 month follow up.

### Gut peptides

GLP-2

Other gut peptides include GLP-2, (which is secreted alongside GLP-1) and acts via another class B receptor (GLP-2R) and is also secreted after eating. Both GLP-1 and GLP-2 are derived from pro-glucagon which is post translationally processed by pro-hormone convertase 1/3 in the L cells. (153, 154)

Intact GLP-2 (1-33) is also cleaved by DPP-4 at the alanine position 2 ( half life of about 7 minutes in the circulation) to GLP-2 (2-33). In a study comparing meal ingestion and GLP-2 infusion versus subcutaneous injection in healthy human volunteers, about 69 percent remained intact one hour after injection. (155)

GLP-2 receptor is expressed in the enteric neurons but also in the central nervous system.

In contrast to GLP- 1 and GIP, GLP-2 is known as an intestinotropic factor. It acts on the intestinal crypt compartments and both stimulates proliferation and inhibits growth.(156)

In a human study of 8 patients without a terminal ileum or colon, intestinal absorption of energy, weight, lean mass, crypt depth and height all improved after 5 weeks of treatment with subcutaneous GLP-2. (157) A DPP-4 resistant analog has been used in the treatment of short bowel syndrome in humans since 2012. Though, it is unclear how GLP-2 acts, effects seem to be indirectly mediated through the ErbB receptor system,(158) Keratinocyte growth factor (released from subepithelial myofibroblasts) (159) and IGF-1 (by enhancing IGF-1 messenger RNA expression and IGF-1 secretion.(157)

The first human study to look at GLP-2 and its effect on bone showed increased areal spine BMD in patients with short bowel syndrome with no terminal ileum or colon (157). In a different study, osteocalcin levels showed no change but CTX levels decreased in a goup of healthy post menopausaul women following a subcutaneous infusion of GLP-2 suggesting a dose dependent decrease in bone resorption. Parenteral admimistration of GLP-1 and GIP in the same study did not result in reduced bone resorption. (160)

When comparing prolonged exposure with high doses, reduced bone resorption was more effective in reducing CTX levels. Overall, GLP-2 seems to inhibit resorption with minimal impact on bone formation with a resultant increase in bone density though the mechanism of how this occurs is still unclear.(161)

Peptide YY

The enteroendocrine L Cells also secrete another hormone peptide YY (PYY) after food which has an impact bone on appetite as well as bone metabolism. It is a part of the pancreatic polypeptide family alongside neuropeptide Y (NPY) and pancreatic polypeptide (PP). It is a 36 amino acide peptide and after degradation by DPP-4, forms the PYY (3-36) (162) . It expresses itself through 4 different G protein coupled Y receptors with the PYY (3-36) binding only to the Y2 receptor in the hypothalamic arcuate nucleus. It is this form which works along with GLP-1 to induce satiety, decrease food intake and play a role in the weight loss seen after bypass surgery.(163)

In a study of 25 healthy men, while single infusions of GLP-1 and PYY had no impact on energy intake, the infusions together worked synergistically to reduce appetite.(164)

In a study of adolescents comparing amenorrhoeic athletes with eumenorrhoeic athletes and non-athletic controls, PYY was higher in the girls with amenorrhoea and they also had a lower BMI and a higher proportion of those with disordered eating. The higher PYY was a negative and independent predictor of PINP (marker of bone formation) and apparent bone mineral density at the lumbar spine. (165)

Elevated fasting PYY has also been seen in women with eating disorders and this was negatively correlated with BMI as well as bone mineral density especially at the spine. (166)

Higher levels after meals have also been seen post gastric bypass surgery (correlating with changes in CTX, a measure of bone resorption) suggesting that PYY could play a role in the bone loss seen after weight loss surgery. (167)

Rodent studies have shown contrasting results with one PYY knock out mice model showing increased osteoblast activity and greater trabecular bone mass (168) with another study showing the opposite effect.(169)

Pancreatic polypeptide (PP)

Pancreatic polypeptide is produced mainly by the endocrine islet cells under vagal control but also in smaller amounts in the exocrine pancreas, colon and rectum in response to both nutrient ingestion and insulin induced hypoglycemia through the Y4 and Y5 receptors and remains elevated for several hours under stimulation by the vagus nerve.(170) Infusion of PP in healthy human volunteers (randomized placebo controlled crossover study in 10 adults ) has shown a sustained decrease in food intake (25.3%). (171).

It is unclear what happens to PP in obesity with studies showing conflicting results. (172). Obese children with Prader Willi syndrome have completely abolished PP secretion.

When fasting levels were checked in 38 obese children and 35 lean controls matched for age, gender and puberty, significantly decreased levels of PP were seen in the obese children which negatively correlated with their BMI. However, a year later following participation in a weight loss intervention programme, the children who lost weight showed a significant increase in their PP levels. (173)

Decreased levels in obesity could be a cause or a consequence due to its impact on appetite and further research is needed to elucidate this.

Cholecystokinin

Cholecystokinin or (CKK) is produced in the ‘l’ cells of the duodenum and jejunum in response to intake of nutrients, particularly fat. CKK is related to gastrin and has several different molecular forms with different number of amino acids. The main mechanism by which CCK suppresses appetite is gall bladder contraction, slow gastric emptying and increasing pancreatic secretion. (174) CCK is also present in different parts of the brain (thalamus, hypothalamus, cortex, amygdala, hippocampus, septum, basal ganglia and dorsal hindbrain). (175)

Some studies show elevated levels in obesity when compared with lean controls and decreased in anorexia nervosa (30 women with AN, 23 with obesity and 25 lean women as the control group). (176) Significant and rapid weight loss (10 percent) following a low-calorie diet for several weeks resulted in a drop in post prandial CCK levels which was maintained a year later. (177)This mechanism however may swing the balance in favour of weight regain which is often seen following weight loss.

Currently, the role of CCK and pancreatic polypeptide in bone metabolism if any is not clear.

Much of the work on some of gut peptides is experimental and is in animal studies. In a predominantly clinical study with a small size, realistically studying all the gut peptides is not possible. As GLP-1, GIP (the two incretin hormones) and ghrelin (the only orixegenic gut peptide) are the most widely studied of the gut hormones with several studies exploring both changes in obesity and diet and surgical induced weight loss in adults, with clear associations with bone metabolism, it seemed reasonable to focus on these for our study.

In the next chapter, we discuss the impact of obesity on bone in both adults and children and the changes seen after rapid and significant weight loss. We also discuss some of the bone formation and resorption markers we measured in this study, changes in which may explain some of the impact seen on bone in obesity and subsequent weight loss.

As one of the concerns about rapid and significant weight loss is the impact on bone and more specifically the growing skeleton in young people, we measured total body and lumbar spine bone mineral density and bone mineral content at all 3 time points. As DXA cannot differentiate between bone compartments or delineate bone strength, we also used the more novel HRpQCT at the radius and ulna to look at changes in the cortical and trabecular compartments.

## Fat and Bone

### 4.1 Bone growth, modelling and remodeling and gender dimorphism in skeletal development

#### The physiology of bone

To understand the effect of obesity on bone, a basic description of bone physiology as well as hormonal control of bone turnover is discussed. There is now recognition that the skeleton is a complex dynamic organ controlled by feedback with multiple factors controlling the remodelling process and holding it in a steady state. In adults, bone remodelling is the main process maintaining the homeostasis while in children, the main process is bone modelling resulting in net gain in bone growth. (178)

#### Bone modeling

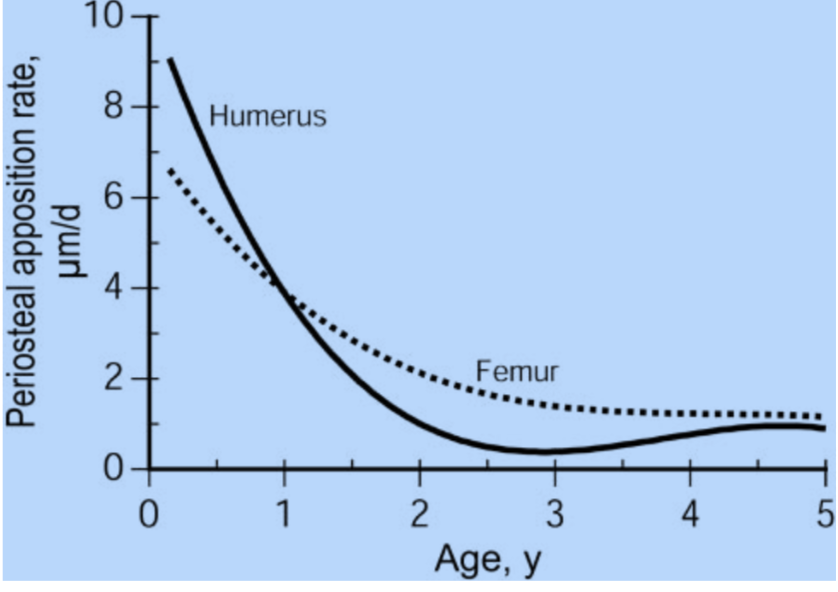
The main process used to shape bones in children who are still growing and to increase the size of the bone at any age following mechanical loading of the skeleton is bone modelling. This results in a net gain in bone with bone growth at the epiphysis but also increase in the thickness of the bone. The length of the bone increases by a process called endochondral ossification during which the cartilage of each bone contributes to longitudinal growth and is gradually replaced by bone. During this process, chondrocytes first proliferate followed by hypertrophy and death. Blood vesssels, osteoblasts, osteoclasts and bone marrow cells then invade the extracellular matrix and lay down bone.(179)

The skeletal diameter of the bone increases by expansion of the osteogenic layer of the periosteum and this is known as periosteal apposition. Bone growth thus occurs both in length and width and these have opposite effects on the bone strength and the bone’s abilty to cope with loading. The periosteum surrounds the bone and continues right upto the growth plate.(180)

X rays of the mid shaft of long bones are the source of most of the information available about bone modelling. Garn et al measured the width of the second metacarpal in several healthy subjects and showed that periosteal apposition rates followed similar rates to standard height velocity charts with rapid growth in early life, then a nadir followed by a pubertal peak and then practically no periosteal growth.(181)

The Figure below shows the periosteal apposition growth in the humerus and femur of boys upto the age of 5. Both bones also show dissimilar rates of growth with the humerus dominating initially followed by the femur later when a child starts to mobilise mirroring a child’s gross motor development.

Figure - Periosteal apposition growth in the humerus and femur in boys upto age 5 years



As the periosteum expands, bone resorption also takes place on the endosteal surface which results in the expansion of the bone marrow cavity. Overall, however there is gain on the periosteal surface compared to the endosteal surface.

Periosteal apposition increases bone width in prepubertal boys and girls; during puberty, this process is accelerated in boys with a lesser degree of endocortical expansion which leads to an increase in the diameter of the bone and the medulla and thickening of the cortex. However, in girls, the periosteal apposition is inhibited during puberty (due to oestrogen) while the endocortical bone formation is stimulated which narrows the medullary cavity while increasing cortical thickness. (182) This later results in the increased bone strength seen in males as more strength is conferred on cortical bone developing further away from the neutral axis.(183)

Studies have shown that the increase in trabecular BMD during puberty is not down to the change in material density as this only changes by 3 % during one’s lifetime.(184)

In a histological study looking at 58 healthy white human subjects between 1.5 to 23 years, compared with adults, growth in trabecular bone was down to increase in bone volume and trabecular thickness but not number, wall or interstitial thickness.(185)

#### Bone remodeling

The interaction between osteoblasts and osteoclasts governs the continuous removal and replacement of bone. The mineralised bone is removed by the osteoclasts which is then followed by the formation of bone matrix through the osteoblasts which then becomes mineralised. Bone remodeling is important not only to change the bone architecture based on ongoing mechanical needs but also to repair any damage to the bone matrix. (186) About 1/5th of trabecular bone undergoes remodeling at any given time in an adult with it taking about two years for each surface to be renewed. (187)

The process starts with the activation of haematopoietically derived osteoclasts while the osteoblasts are derived from the mesenchyme; the predictable nature of the process indicates that communication exists between the osteoblasts and the osteoclasts such that when one goes up, the other follows (178).

Once, the role of osteoblasts in bone formation is complete, they develop into osteocytes which are the most abundant type of bone cell. (188)

The activation, differentiation (dependent on macrophage colony stimulating factor M –CSF and receptor activator of nuclear factor –Kb (RANK) ligand) and eventual destruction of the osteoclasts depends upon both hormonal as well as local factors.

There is a clear relationship between osteoclastic resorption and osteocyte apoptosis. In a study looking at the impact of creating bone fatigue leading to matrix damage in the ulna of adult rats, changes in osteocytes indicating damage were seen a day after loading.(189). The osteocytes form a functional syncytium by gap junctions (called the bone basic cellular sysyem BBCS) extending from the bone to the vessels which can recognise both mechanical strain and biochemical factors which drive bone formation and resorption (190). After the apoptosis, activated bone lining or stromal cells release M-CSF which is then the signal for osteoclastogenesis. (191)

#### Age related changes in children’s bones

Some studies report that similar gains in total body and regional bone mineral content are seen in both sexes till between 14-16 years. In a large cross sectional study of 207 healthy Caucasian children when bone variables (bone mass, bone mineral content, bone mineral density) were compared with young adult reference values, bone mass accrual peak corresponded to the same pubertal stages in both boys and girls. (192) Thus, the difference in timing of peak bone mass accrual in gender is due to the difference in the timing of puberty in the two sexes.

In another longitudinal study, the marked increment was seen in the spinal bone mass in girls between the age of 11-14 years, however, this fell dramatically fell at 16 years or two years’ post menarche. Whle in boys, the period of gain was later and longer from 13-17 years but still continued uptill age 20.(193)

Higher mean values at the end of growth were seen in boys for L2-L4 BMC and Femoral neck and femoral shaft BMD but not for L2-L4 BMD.

Slow progressive increase in both total body and site specific bone mass continues for several years ater after peak bone mass accrual with the plateau in bone area occurring a couple of years before that of bone mineral content. (194)

BMC and BMD at the femoral neck and femoral shaft also reach peak values earlier in girls which is similar to what is described in the lumbar spine but there is also a rapid reduction after the age of 15 years while femoral bone mass accrual is sustained beyond 15 years in boys (195).

Volumetric bone mineral density of long bones (both radius and femur) is same in both boys and girls throughout childhood in both calculations made from DXA measures and peripheral quantitative computed tomography studies. This lends credence to the discussion that the aBMD increase seen during growth could be due to an increase in bone size and cross-sectional area rather than a true gain in density and that these measurements may not be valid in the paediatric population. (196) (197)

However, the volumetric bone density between L1-L4 remaineds age and growth dependent related to an increase in trabecular density suggesting that axial and appendicular bone may respond differently to stimuli in adolescence.

There are racial differences as well with vertebral bone density and femoral cross sectional area at end of puberty almost 11 and 6 perecent higher respectively in black children which could have longer term implications for bone fragility. (196)

Thus, growth over all produces a bigger but not denser skeleton in males and females but the pattern of growth offers some advantages to the male skeleton which allows better adaptation to aging and protection from bone loss and fracture risk.(198)

### The relationship between fat and bone in adults and children: differences/paradoxes

The prevailing obesity epidemic has raised concerns about both the effect of obesity as well as its treatment on the growing skeleton.

#### Effect of obesity in bone-adults

The effect of fat on bone is controversial in both adults and children with different studies showing conflicting results.

It was previously thought that obesity is protective of bone health and that long term weight bearing strengthens bone, resulting in increased bone mass in adults(199).

However, more recent evidence suggests that osteoporosis and obesity can occur together with lower bone mineral density and reduced bone formation rates seen in subjects with higher percentage of body fat (200). The effect of fat on bone may also be site specific with visceral fat leading to compromised bone structure and strength and an increased fracture risk in both younger and older adults. Subcutaneous fat may have the opposite effect(201). Vertebral end plate depression and an increase in the number of compression fractures have been associated with increased bone marrow fat. A pilot study of 26 adults looking at bone marrow fat and BMD using DXA and proton MR Spectroscopy showed that a bone marrow fat/BMD ratio could be used as an indicator of bone weakness(202). They were not able to prove an inverse relationship between BMD and bone marrow fat but bone marrow fat could be used to diagnose reduced bone strenth almost as well as BMD.

Though not entirely clear, the adverse effects of obesity on bone may be mediated by a number of mechanisms including the causes and consequences of visceral obesty and metabolic syndrome (MS associated with lower BMD, More osteoporotic non vertrebral fractures in MS) (203)as well effects of bone marrow fat(114) as both osteoblasts and adipocytes differentiate from the same precursor.

Vitamin D deficiency is also very common in obesity due to poor diets high in calories but with inadequate consumption of food products and supplements containing Vitamin D, and reduced exposure to the sun(204). There is also decreased bioavailablity because being fat soluble, Vitamin D gets sequestered within the large amounts of adipose tissue.

Hyperparathyroidism is also common in obesity independent of the vitamin D deficiency, though this will also play a role. Cross sectional study on 236 adolescents undergoing evaluation for bariatric surgery showed that more than half were Vitamin D deficient and only 18 percent had normal levels. African American teenagers and those with the highest BMI had the greatest risk(205). We measured Vitamin D levels at baseline, at 6 months at balloon removal and then at 24 months. The young people were advised to take 1 multivitramin capsule daily containing 400-1000 IU of Vitamin D.

#### Positive effect of obesity on bone in children

The relationship between fat and bone in children is unclear. This is further compounded by the effects of growth and puberty with physical activity, and dietary calcium intake having a lesser role.

Many studies report a positive association between body weight and bone mass. In a study looking at bone mineral density in cortical and trabecular sections of the distal forearm in almost 500 young people between the age of 8 and 17, it was clear that age, height and weight were positively related to bone density though it was less clear whether the contribution of weight was due to fat mass or lean mass(206).

The more recent HELENA study which studied 330 Spanish adolescents showed that overweight/obese young people had a higher BMC than their normal weight counterparts; after adjusting for calcium intake, physical activity and pubertal staging, this was explained by their higher levels of lean mass(207).

Obese children also tend to grow faster and go into puberty earlier as compared to their non-obese peers and therefore the increased bone mass seen could be related to this rather than an actual increase in bone due to the positive effects of their increased weight. This was illustrated in a study where bone mineral content and percentage fat were compared between the obese and non-obese groups. No difference was seen after correcting for height. (208)

A cross sectional study of 450 pre-adolescent girls by Ilich and Skugor looked into this aspect further and showed that bone area, lean body mass, body fat, bone age and calcium intake were the most significant predictors of bone mass(209).

#### Negative effects of obesity on bone in children

However, there is an increasing body of literature challenging the positive effects of obesity on bone, with the majority of the work coming from New Zealand.

Distal forearm fractures are the most common type of fracture in childhood.

A study that looked at 100 Caucasian girls between 3-15 years from New Zealand showed that those who fractured had lower bone density as compared to 100 controls. Those who fractured in the 8-10 year old age group weighed significantly more, though the increased weight was seen across all age groups. (210). Bone size was not significantly different between cases and controls.

In a similar study looking at boys this time, the fracture group had twice the number of overweight children with lower areal and volumetric bone mineral density, lower bone mineral content, and higher fat and lower lean mass compared to the controls(211).

In a study looking at a mixed cohort of both boys and girls with 2 or more fractures (295 fractures amongst 90 children and adolescents), Z scores for weight, BMI, fat mass and fat percentage were all higher while z scores for BMC and BMD at the ultradistal radius were lower when compared to a reference population(212).

There is also evidence to show that these weaker skeletons persist over time with a lower bone mineral content (2-5. 7 percent) evident on DXA scanning (total body, lumbar spine, ultra distal radius and hip trochanter) in girls with previous fracture four years down the line(213).

In obese adolescents, bone mass relative to body size is reduced and there is increased prevalence of forearm fractures(214). In a cross sectional study performed at Sheffield Children’s Hospital NHS Foundation Trust comparing obese and non obese children and stratified further based on the history of prior fracture, 18 percent of obese children fulfilled the criteria for osteoporosis. The total body areal BMD, lumbar spine areal BMD were significantly lower in obese children with prior fracture(215).

#### Relationship between changes in bone mass and fat mass over time in children

A number of studies also suggest that the relationship between fat and bone changes from early childhood into the teenage years with higher fat mass having a positive effect on bone in prepubertal children but changing to an adverse effect during puberty(216, 217).

In a study of over a 1000 children, bone mineral density was assessed in the second metacarpel of the left hand and both obese boys (age 7-11) and obese girls (aged 7-9 years) were shown to have a higher mean BMD than the children with normal BMI. But in young people>12 years, percentage fat mass negatively correlated with BMD and the mean BMD was lower than controls(216).

Other studies have highlighted that it is the fat distribution that determines the impact on bone. Ethnicity, gender and puberty may also play a role. In a large study in Alabama, 181 pre-pubertal children (116 girls, 65 boys, 99 Caucasian and 82 Afro-American) had DXA scans to determine total body and truncal fat mass and bone mineral content (BMC) followed by a single slice CT to determine subcutaneous abdominal adipose tissue (SAAT) and Intra-abdominal adipose (IAAT) tissue. They found that truncal weight was inversely correlated with bone mineral content in both groups. However, more specifically in the Caucasian children, it was the SAAT and BMC that were inversely correlated (r=-0. 58, p<0. 0001) with SAAT explaining 6 percent of the variance in BMC and in the Afro-American children, it was the IAAT and BMC that were inversely correlated (r=-0. 5, p<0. 01).

The Avon Longitudinal study of Parents and Children (ALSPAC) from Bristol which has also explored the impact of fat mass on bone showed that children who had a smaller skeleton relative to their body size tended to fracture more(218). The study involved doing a DXA scan for over 6000 children at age 9. 9 years and then following them through for 2 years for fractures and looking at links between the two.

Cross sectional analysis in the same group showed a strong positive relationship between total body fat mass and TBLH bone mass and area which persisted after adjusting for height and lean mass in both boys and girls but this association was not seen at the start of puberty in tanner stage 2 girls and in fact switched to being negative in tanner stage 3 girls, again highlighting the changing relationship between fat and bone during different periods of growth.

We have used Whole body DXA and lumbar spine parameters in this study to evaluate the changes over the 3 time points. All our young people were Tanner stage 4/5 in puberty status and had completed much of their growth. Physical activity was assessed by self-report and therefore somewhat subjective. While advice was given regarding portion sizes, balanced meals and a daily multivitamin capsule was recommended containing RDA (|required daily amounts) appropriate for age, we did not quantify the amount of calcium in their diet.

#### Effects of weight loss on bone in adults

As well as the effects of obesity on bone health, concern has risen in recent years about the impact of weight loss interventions on bone. A 1-2% bone loss has been seen at different skeletal sites following a 10% weight loss (which is considered to be clinically significant), in various studies in adults(219, 220). Bariatric surgery patients experience weight loss far excess of what has been previously seen with lifestyle and pharmacological interventions. There is considerable evidence now that bariatric surgery results in changes to bone and mineral metabolism accelerating bone loss(114). Proposed mechanisms that underpin this include reduced mechanical loading (seen in other populations like spinal cord injury or bed rest as well), changes in calciotropic hormones (PTH, Vitamin D ) as well as gut hormones as discussed previously. A retrospective cohort study in the UK however did not find an increased risk of fracture in over 2000 patients post bariatric surgery (mostly banding) when compared to over 10442 match controls. Although only followed up for 2 years, trends of increased fracture risk had started to become clearer in those who lost the most weight(221).

Another retrospective study from the USA which had a longer median follow up of 7. 7 years compared fractures in the bariatric surgery group (94% bypass, 258 people) with the background population and found that the group who underwent surgery had a 2. 3 fold higher relative risk of any fracture. Half of all fractures were lower limbs or hand with Vitamin D deficiency and levels of activity prior to the procedure being good predictors of fracture incidence (222).

There are several potential mechanisms to explain the bone loss seen after weight loss.

1. Restricted energy intake, reduced delivery of essential vitamins and minerals such as calcium and Vitamin D further exacerbated by pre-existing deficiencies which are common in obese patients (223) can lead to secondary hyperparathyroidism and consequent metabolic abnormalities. Most studies also fail to ensure that patients take their supplementation rigorously and there is also great variation in dosage schedules.
2. Reduced mechanical loading of the skeleton as a consequence of the weight loss is another theory that could contribute to increased bone turnover and reduced bone mass(224).
3. Hormonal changes following bariatric surgery can also lead to the associated bone loss. Recent studies suggest that there is altered secretion of hormones from adipose tissue and (adipokines such as leptin and adiponectin) and from the gastro-intestinal tract (GLP-1, ghrelin) after rapid and significant weight loss, all of which have a role in bone metabolism.

We therefore measured several bone formation and bone resorption markers at baseline (before balloon insertion), at 6 months (after balloon removal) and 18 months after to look for changes which may mediate further changes in bone mineral density, bone architecture and strength.

#### Effect of weight loss on bone in children

Twenty six percent of adult bone mass is achieved during adolescence through peak bone mass accrual and this predicts later osteoporotic risk (192). Increasing the bone mass acquired at this time is equally if not more important than slowing down bone loss in the older age group to reduce risk of fracture. Significant weight loss at the time of peak bone bone acquisition whether by diet/pharmacotherapy and now increasingly by surgery may therefore profoundly reduce bone mass accrual. However, paradoxically it could improve the negative effect of obesity on bone in children seen post puberty, with weight loss leading to increased bone mass relative to body size and reduce the risk of fracture.

Only one study to date has demonstrated the effects of profound weight loss on bone in adolescents following obesity surgery. A study in 61 adolescents who had RYGB showed significant bone loss with a 7. 4 % decrease in bone mineral content and a decrease in the Z score from 1. 5 to 0. 1, though this was still within normal values for age and gender. This is likely to be due to the higher starting point for this group of extremely obese adolescents. We need to find out whether bone loss in young people with obesity following surgical intervention continues, becomes stable or improves once the adverse effects of obesity are removed. Some of the limitations in this study which may have underestimated the degree of bone loss were that they excluded young people at the extremes of morbid obesity (weight limit 136 kg and 159 kg at different time points in the study for the DEXA machine used), a number of young people did not have scans prior to surgery and Whole Body DXA measurements were used to measure bone mineral content and bone density which is perhaps not as good as regional scans for predicting fractures at specific skeletal sites(225).

In another study in adolescents, weight loss (following treatment with sibutramine and diet control) led to a decrease in appendicular (limb) bone mass but a paradoxical increase in spinal bone mass suggesting that the impact of weight loss on the growing skeleton may be region specific or may result in a redistribution of bone from the appendicular to the axial skeleton(226).

#### Bone formation markers

The balance between bone formation and bone resorption is what determines the bone mass, and bone mineralisation.

Osteoblasts produce bone formation markers during different phases of their development and these can be measured in serum or plasma.

These include:

1. By products of collagen synthesis (P1CP at the C terminal and P1NP at the N terminal)
2. Total and bone specific alkaline phosphatase
3. Osteocalcin (a matrix protein)

P1NP is a 35 kDa aminoterminal propeptide of type I collagen and is obtained by post translational cleavage mainly from proliferating osteoblasts and fibroblasts. P1NP exists as a trimeric or monomeric form and immunoassays either detect the trimeric or the total which is what we did in our study using the Roche modular analytics E170 analyser.

The range for P1NP is said to be higher in males under <25 years of age due to bone growth (227) but is generally quoted between 15-80 microgram/L based on an Australian study with about 2500 people. For females, the ref range for those less than 30 years was 25-90 microgram/l.

P1NP is better than P1CP as a measure as it is not affected by pituitary or thyroid disease and its assay has low inter individual variability, minimal circadian variation and is stable at room temperature(228). We measured P1NP at baseline, at 6 months’ post balloon removal and 18 months thereafter. This was done first thing in the morning on an empty stomach as participants were coming in fasted for the OGTT.

Alkaline phosphatase is an enzyme found in the plasma membrane of osteoblasts. It has an important role in bone formation and mineralisation by degrading pyrophosphate which inhibits mineralisation in an alkaline pH. It has several iso-forms in liver, placenta and bone with the bone form sensitive to temperature.

We measured only total alkaline phosphatase in this study as a part of the bone profile at the 3 time points.

**Osteocalcin:** Osteocalcin is an established marker for bone formation. It is made by the osteoblasts, odontoblasts and hypertrophic chondrocytes through the Ocn gene and is the main non-collagen protein found in the extracellular matrix(229). It has 2 different forms: the carboxylated (active form in bone) and uncarboxylated form. The uncarboxylated form has a role in energy metabolism and helps with insulin secretion and beta cell proliferation in the pancreas and increases adiponectin secretion from the adipocytes. Carboxylated Osteocalcin is a late marker of osteoblastic activity and is difficult to interpret due to being impacted on by Vitamin K, kidney function, the circadian rhythm and its short half-life(228).

The effect of obesity on osteocalcin is still unclear.

Some studies report no differences between obese and children with normal BMI (230) while others report lower values in obese 5-18 year old girls. In a study looking at 150 obese children and adolescents, 1/3rd had metabolic syndrome but no association was seen between insulin resistance, metabolic syndrome parameters and osteocalcin levels. (231) However, another study with similar numbers showed a mean osteocalcin level of

7220. 5 microgram/l and after correcting for confounders, showed an inverse relationship with HBA1c, HOMA-IR, triglycerides and waist circumference. (232)

The figure below shows the bone formation and resorption markers released during modelling of bone.

Figure 9 - Bone remodeling

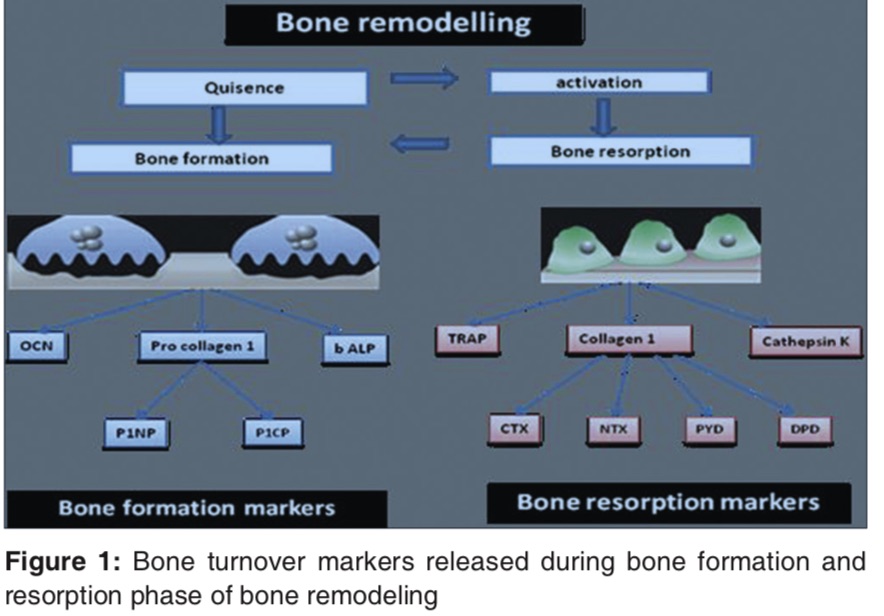


Figure 8: From Shetty et al Bone Turnover markers: Emerging tool in the management of osteoporosis(228).

#### Bone resorption markers

Bone resorption markers can be categorized as follows(228)

1. Collagen degradation products – (urine and serum)

* Telopeptides of type 1 collagen (CTX-1 and NTX-1)
* Hydroxyproline
* Pyridinum crosslinks

1. Non-Collagenous proteins like bone sialoprotein
2. Osteoclastic enzymes

* Tartrate resistant acid phosphatase
* Cathepsin K

1. Osteocyte activity markers which include (serum markers)

* Receptor activator of nuclear factor kappa-B ligand (RANK-L)
* Osteoprotegerin (OPG)
* Dickkopf-related protein 1 (DKK-1)
* Sclerostin

Bone resorption is the function of the osteoclast whose differentiation is regulated by macrophage colony-stimulating factor, RANK ligand and osteoprotegerin (OPG)(233).

OPG and RANK-L are both derived from osteoblasts. RANK-L is activated by B and T cells and is important for osteoclastogenesis, however its activity can be neutralised by binding to the soluble decoy receptor OPG. This system comes into play relatively late and helps to maintain the balance between bone formation and resorption(234).

DKK-1 is secreted by osteocytes and inhibits formation of bone by inhibiting the WNT signalling by binding to the LRP-5 receptor in the osteoblasts(235).

CTX results from the degradation of type 1 collagen. Native CTX has 2 form; alpha and beta which undergo further isomerisation to form D and L forms. With protein aging, beta isomerisation of the alpha forms occurs and altered ratios suggest new bone formation in growing children and diseases like Paget’s, malignancy etc. The main issue with CTX is the circadian variation. CTX levels can drop by almost 20 percent after eating; we collected the samples first thing in the morning after an overnight fast to avoid this. NTX is generated by cleavage of the N terminal region of the amino terminus of type 1 collagen by cathepsin K during bone resorption. CTX and NTX can be measured in both serum and urine(228). Urine NTX has less circadian variation and post meal variability than CTX.

Our team at Sheffield has shown previously that OPG (which is inversely proportional to leptin and total body and truncal fat mass) is lower in obese children allowing unopposed action of RANK-L, and thus could play a role in the increased bone resorption seen in obesity (236).

CTX was also noted to be significantly higher in the obese group and correlated positively with the leptin.

Conversely, in a study comparing bone turnover markers in 26 Japanese girls with anorexia nervosa and their healthy matched controls, there was higher OPG relative to a reduction in leptin, oestrogen levels and BMI and the OPG could thus be mitigating the bone loss seen(237).

Some studies have shown that decreased leptin levels after bariatric surgery are related to an increase in bone turnover markers like serum NTX suggesting that leptin may mediate the increased bone catabolism seen after weight loss(132).

We measured serum PINP, osteocalcin (from the bone formation markers group) and RANK-L, OPG, DKK-1, and Urinary CTX and NTX (bone resorption markers group) in this study.

There is a lot of variability in the bone turnover markers due physical activity/menstrual cycle/seasonal variation/circadian variation/fasting and meals etc as mentioned for some of the above and therefore the samples were all collected in the morning after an overnight fast when participants were attending for an OGTT(238).

### Gut hormones and bone

Apart from the effect of adipokines on bone following significant weight loss, another potential mechanism by which bone metabolism could change is due to gut hormones, the levels of which also change after significant weight loss following diet/pharmacotherapy or bariatric surgery. The gut hormones of particular interest are the incretins, GLP-1 (Glucagon like peptide -1), GIP (Glucose dependent insulinotrophic peptide) and ghrelin.

The effect of GLP-1 on bone remains unclear. GLP-1 receptor knockout mice show cortical osteopenia and bone fragility with increased number of osteoclasts(239). In another study, rats (both normal and glucose intolerant) treated with exogenous GLP-1 showed an increase in the expression of osteoblastic genes in bone tissue raising the possibility of using GLP-1 as treatment in improving osteoporotic changes associated with diabetes(123).

GIP, secreted by the K cells in the proximal small intestine is also emerging as a possible modulator of bone metabolism. GIP receptor knock out mice have a blunted insulin response to feeding, low bone mass, reduced bone size and poor trabecular structure due to reduced bone formation and increased osteoclast activity (240).

Ghrelin may also have a role in bone metabolism through its effects on growth hormone and insulin like growth factor- 1 as the growth hormone secretagogue receptor also binds ghrelin and is expressed by osteoblasts as well(241). Increased BMD is seen in Ghrelin-infused rats though ghrelin knock out mice have unaltered BMD and BMC (242, 243).

With a number of different conclusions coming from animal and some human studies, delineating the roles of adipokines and gut hormones in bone metabolism and finding out whether/if any changes occur in their secretion following significant weight loss and if this was sustained over a period of time was considered timely.

Therefore, in parallel to our study looking at the metabolic consequences of intra-gastric balloons surgery,we performed a sub-study to examine the impact of rapid and significant weight loss following intragastric balloon surgery on bone mineral density, bone mineral content and fat/lean mass using DXA and on a variety of adipokines, osteokines and gut hormones.

We explored the association if any between the changes observed in adipokines, osteokines and gut hormones to explain possible changes in bone mineral density and skeletal micro architecture over a 24 month period.

### DEXA and HRpQCT

Although, DEXA has long been used to examine the relationship between fat and bone, concerns have been expressed regarding the accuracy of DEXA analysis particularly in severe obesity(220). DEXA analysis provides two dimensional information which is interpreted 3 dimensionally using various corrections for body size. DEXA however cannot measure volumetric bone mineral density or bone microstructure that defines bone strength, nor can it differentiate between trabecular and cortical bone(244).

The recent introduction of high resolution peripheral quantitative computed tomography (HRpQCT) has allowed the in-vivo 3D study of cortical and trabecular structure of bone in humans to a resolution of 82 micrometres (Xtreme CT1) (figure 2) (245). This technique has advantages over DXA. Second-generation HR-pQCT scanners, such as the XtremeCT II, can image the bone at a resolution of 61 micrometres whilst reducing the image acquisition time from 3 to 2 minutes.

The Mellanby Bone Research Unit at the Northern General Hospital in Sheffield has one of only four clinical Xtreme CT1 scanners in the UK.

The measurement variables acquired using the XtremeCT I scanner include total, trabecular and cortical vBMD and area, cortical porosity, and trabecular number, thickness, separation and inhomogenity. We also have expertise in the application of microfinite element (microFE) analysis methods to HR-pQCT images which enables us to acquire detailed information about bone strength. Bone density, structure and strength are all key elements in the determination of fracture risk

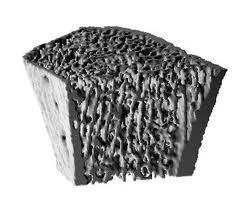
(246).

Only recently has normative data become available in terms of age, sex and ethnicity specific centile curves for adolescents. In a Canadian study , 349 young people ( 10 to 21 years old) were scanned once a year for a maximum length of four years (May 2008 to June 2012) and both standard as well as augumented measures were reported(247).

The Bone strength increases (accelerated in boys) during peak growth periods is due to increases in bone area and bone mineral density at metaphyseal and diaphyseal sites but this is also accompanied by changes in bone microarchitecture.

The plan thus is for our patients to undergo serial radial and tibial HRpQCT imaging over two years to define skeletal density, microstructure and strength in relation to changes in body proportions and percentage fat mass (body composition) determined using DXA.

Figure 10 - Representative HRpQCT images of the radius with separation of the the cortical and trabecular bone compartments (left) and a cross-section view (right)

Therefore, from the bone aspect we want to:

1. Examine the change in bone mineral content, lean mass and fat mass following IGB placement as assessed by DEXA.
2. Examine the cortical and trabecular bone density, architecture and strength using HRpQCT in severely obese adolescents and find out how weight loss and HR-pQCT measurement variables are asssociated with IGB placement.
3. Examine expected changes in leptin, adiponectin and ghrelin with weight loss and their impact on bone turnover if any.
4. Examine changes in baseline and stimulated GLP-1, GIP levels after weight loss and find out if these corelate with changes in bone as assesed by radiographic imaging and bone turnover markers?

Defining the effects of obesity followed by weight loss on skeletal integrity in morbidly obese adolescents may direct therapies that specifically improve both cortical and trabecular bone mass. This may prevent the increased fracture risk seen at this time and offer us interventions that extend beyond the simple supplementation of dietary vitamin D and calcium.

### Summary

It is clear from the review so far that childhood obesity is a significant health concern. Gaps exist in the management of severe childhood obesity and intragastric balloons may be efficacious at least in the short-term in facilitating weight loss in adults. This may not be wholly maintained in the longer term; however, BIB may still result in improved health outcomes and a reduction in co-morbidities associated with obesity.

Our hypothesis is that the short-term use of intragastric balloons in a paediatric population will serve as an aid to promote initial weight loss. This has been demonstrated in adult populations. The use of intragastric ballooning in combination with a behaviour management program will serve as a tool with which to facilitate further weight loss and in the long-term will help individuals reach and maintain a healthy BMI. This approach has advantages over currently available treatments. It is possible that a reduction in co-morbidities and a lowering of mortality rates associated with obesity can be achieved with intragastric ballooning. The fact that it is a temporary procedure may make it more acceptable in paediatric populations.

This in combination with a behaviour management program will serve as a platform to facilitate reduced longer term BMI compared to currently available treatments. The lower mortality associated with intragastric balloons and the fact that it is a temporary procedure may make it more acceptable in paediatric populations.

However in order to work towards a full RCT to assessing the efficacy of either intragastric balloons alone or to compare balloons with pharmacological therapy (orlistat) or bariatric surgery, a feasibility study is needed to assess the magnitude of weight loss, the degree of maintenance of weight loss potential, and impact on longer term health.

During this study, we looked at a range of secondary outcomes such as impact of weight loss on metabolic data, co-morbidities such as blood pressure, and insulin resistance. As this procedure is being conducted during a time of peak bone mass accrual, we also assessed changes in bone mineral density using DXA and changes in bone microarchitecture and strength using HRpQCT. We also measured a variety of gut hormones, adipokines, bone formation and resorption markers to see changes if any in these could have a role in mediating/explaining some of the changes in secondary outcomes such as co-morbidity resolution.

The next chapter describe the aims of the study, the exclusion and inclusion criteria, approvals, funding arrangements, ethics and the day to day running of the study.

## Materials and Methods

### Aims and outcomes

The key aims of our study are:

#### Primary aim

* To establish the potential of the intragastric balloon supported by a lifestyle intervention programme to support weight loss in adolescents with morbid obesity, to obtain estimates of the magnitude of weight loss & to ascertain the extent to which that weight loss is maintained.

#### Secondary aims

* To examine longitudinally the impact of treatment with intragastric balloon on co morbidities such as glucose metabolism, blood pressure, lipids
* To measure baseline and stimulated incretins during the Oral Glucose Tolerance Test (OGTT) and look at changes if any following weight loss following balloon placement.
* To ascertain the effect of weight loss on the health (including bone mass, bone mineral content, bone density and bone architecture) of the developing skeleton.
* To assess the impact of weight loss on psychosocial factors such as an individual’s self-esteem, the incidence of depression, and their overall quality of life by using validated questionnaires. To determine what outcomes adolescents, consider most important-this work was led by the exercise and science officer at Sheffield Hallam University.

#### Primary outcome measure

The primary outcome measure will be:

Change in body weight and change in BMI standard deviation score from baseline following six months’ intra-gastric balloon therapy and subsequently at 18 months’ post balloon removal.

Alongside this, we will review a host of secondary outcomes at outlined below.

Secondary outcome measures

1. Biomedical outcomes comparing change in biomedical data at the various time points (baseline, following six months intragastric balloon therapy and subsequently at 18 months’ post balloon removal):

* Difference in fasting glucose, fasting insulin, Area under the curve, HBA1c and HOMA
* Difference in total cholesterol, triglycerides
* Difference in systolic and diastolic blood pressure standard deviation scores.
* Change in liver function tests
* Changes in Ghrelin, GLP-1 and GIP levels
* Changes in adipokines, ghrelin
* Change in osteokines, bone formation and resorption (turnover) markers

1. Changes in total fat mass, bone mineral content and bone mineral density as assessed by DXA
2. Changes in bone density, architecture and strength as assessed by HR pQCT.
3. Changes in Psychosocial measures from baseline following six months intragastric balloon therapy and subsequently at 6, 12 and 18 months post balloon removal-subject of lifestyle and exercise science officer’s thesis- subject of lifestyle and exercise science officer’s thesis(248).
4. Changes in Physical fitness and physical activity as measured by modified Balke protocol and changes in scores on the Physical Activity Questionnaire for Adolescents - subject of lifestyle and exercise science officer’s thesis(248).

### Study design

The study design was discussed within the team as well as at PPI (patient and public involvement) meetings as is the recommendation during the development of the project protocol. The option of both a randomized control trial as well as a cohort study was discussed.

Two patients (aged 13 & 17) and three parents who between them had experience of balloons and bariatric surgery or were considering them collaborated on the study design. Importantly, and this was discussed at the ethics meeting as well, potential participants felt that randomization would not be acceptable. They were very clear that ‘there was nothing in a control study for them’ as all the participants would have failed to lose weight with a traditional weight management programme, previous participation in which was an essential prerequisite to inclusion in the study. Discussions were also held regarding a sham control procedure as well as a sham control procedure with cross over but the time frame, funding and ethical considerations did not allow for this.

Thus, a pilot study design was chosen as the best way to assess if young people could be recruited to such a programme, if the intra gastric balloon was safe and acceptable to the young people, whether the intervention could be delivered successfully, and if it was efficacious in the short and then longer term. This would almost be a pre-requisite to whether a randomised control trial looking at IGB was a feasible further option. Thus, a pilot study design or a ‘vanguard’ study is necessary to provide early evidence regarding an intervention of a yet unproven modality(249)

The natural history of obesity in such individuals is typically one of further weight gain. A cohort design may in fact underestimate the impact of the balloon if the comparator is an individual’s own weight at baseline whereas it’s likely that a control group would demonstrate further weight gain. However, this was felt to be acceptable for a feasibility study.

Therefore, finally a cohort design was adopted after much discussion. A cohort of 12 severely obese adolescents (BMI>3. 5 SDS, puberty stage 4) was recruited to an open non-randomized feasibility study. A BMI of +3. 5 SDS(12) (OSCA) would classify the individual as extreme obesity and is crudely equivalent to an adult BMI of >40 and the threshold criteria for bariatric surgery. (10) American guidelines for surgery in adolescents recommend that individuals should have completed the majority of their growth, which typically occurs by stage 4 puberty (bone age 13 years for girls and 15 years for boys). Individual’s eligibility was checked against a checklist issued by the company. (Appendix 2)

An intra-gastric balloon (ORBERA-manufactured by Allergan, inflated to 500 ml with saline as per manufacturer’s instructions and advice from local bariatric surgeon) was placed in situ endoscopically under general anaesthesia for 6 months. Follow up of patients will continued until 18 months’ post balloon removal.

### Sample size

Sample size of 12 was selected as the optimal size for a feasibility study. This was chosen based on advice from the Research design service at ScHARR (School of Health and Applied Research)(250). It is important in a study of this sort (where there is limited evidence of the efficacy of the treatment modality in a particular patient group), that the requirements of getting data on potential outcomes is balanced with minimizing the numbers exposed to the intervention.

### Recruitment and planning

Recruitment was planned from the specialist endocrine clinics at Sheffield Children’s Hospital as well as surrounding district general hospitals and tertiary centers. Local Community weight management programmes such as ‘SHINE’, ‘More4Life’, were also approached. Letters explaining the project with detailed ‘inclusion’ and ‘exclusion’ criteria with contact details of principal investigator, which were approved by ethics, were sent out. Advertisements to be placed around the hospital and press releases for the hospital website, local and national press were also prepared and approved by ethics and were to be used if required to boost recruitment. However, they were not needed.

Inclusion and exclusion criteria for the project were based on NICE Criteria for bariatric surgery (74)and recommendations from the company.

#### Project Plan

1. Amendment of the original protocol for the project after an extended literature review of the subject.
2. Preparation of the information sheets, consent forms, source data forms, advertisements related to the project and letters informing surrounding hospitals and weight management programmes about the project to help recruitment.
3. Application to and approval from the CLAHRC Independent scientific Review Process (ISR) as the project is primarily funded by them(£100,000).
4. Risk reporting for the Children’s Hospital Trust as per hospital trust policy for any new procedure.
5. Obtaining ethical approval from the Sheffield Research Ethics Committee and subsequent amendments and full final approval.
6. Liaison with the surgical/critical care/A&E/pharmacy/laboratory and anaesthetic teams at SCH.
7. Liaison with the Mellanby Centre for Bone Research, NIHR Clinial Research Facility at the Northern General Hospital, Sheffield for the HRpQCT scans.
8. Liaison with the radiographers at Sheffield Children’s Hospital for the DXA scans
9. Liaison with the trust Clinical Governance and MEMG committee for use of the intra-gastric balloon.
10. Final Research and Development approval from SCH.
11. Applications for top up funding (4 applications made, successful at receiving £15000 from the BSPED in November 2012)
12. Liaison with lab personnel regarding send away samples, as well as with technical help at different companies regarding storage instructions for different samples.
13. PS (PI for project and PhD student) and MAT (paediatric gastroenterologist) attended sessions with RA, adult bariatric surgeon to observe balloon insertion and removal procedure. PS provided liaison between gastro nurses and theatre staff at SCH and Claremont Hospital regarding storage and use of the intragastric balloons.
14. PS liaised with Allergan, producers of the ORBERA balloon regarding order placement via supplies.

The inclusion criteria were those that met the exceptionality criteria of the NICE Guidance for Bariatric surgery. It was important to make clear in all the applications that the balloon was only being offered to the young people who were eligible for bariatric surgery and who had failed at all reasonable conservative attempts to lose weight. That their degree of obesity was such that their mental and physical health were already affected. The exclusion criteria were adapted from the product literature as well as the systematic reviews in the adult population based on safety issues and complications seen in the adult studies.

#### Key Inclusion and exclusion criteria

* BMI> 3. 5 SD roughly equivalent to adult BMI of 40 kg/m2
* Have attained or nearly attained adult stature and stage 4 pubertal development.
* Failed to attain a healthy weight with organized attempts at conventional weight management.
* Agree to avoid pregnancy for at least one year postoperatively (if sexually active).
* Are capable of and willing to adhere to nutritional guidelines postoperatively.
* Are willing to attend weekly support programme.
* Able to give informed assent.

Exclusion criteria (increased risk of adverse event in adult populations)

* Previous oesophageal or gastric surgery or history of intestinal obstruction.
* History of inflammatory disease of the gastrointestinal tract such as oesophagitis, gastric or duodenal ulcers, or congenital anomalies such as atresias or stenosis.
* Hiatus hernia >5 cm (assessed at balloon insertion).
* Significant psychological disorder.
* Pregnancy.
* Bilateral forearm or lower leg fractures- exclusion criteria for the bone aspect of the study but not for the main study.

#### Selection of participants

Following a patient referral from their hospital consultant, a meeting was arranged with the Principal investigator (Dr PS) and the exercise and science officer (LR) from Sheffield Hallam University. A full medical history was taken including past medical history, family history of endocrinological problems as a part of thie assessment following a referral to a teriary children’s hospital.

Accurate height and weight measurements were taken. BMI was calculated from height and weight measurements and then converted to BMI SDS appropriate for age and sex using an online calculator.

Inclusion and exclusion criteria were explained. A detailed over view of the project including the benefits, risks of the use of the intra-gastric balloon were explained. The flow chart of patient visits as well as information leaflets for the parents and age appropriate information sheets for the young people (13-16 years, 16+) were given at this meeting. Some families (if they preferred) had the information sheets emailed to them before they come for the preliminary meeting.

Asking the girls their age at menarche was used as an assessment of pubertal stage. The boys were asked to choose the picture that best described their stage of puberty using a validated line diagram. (appendix 9) If there was concern re maturity, an x-ray was performed of the left wrist to assess bone age by Tanner Whitehouse system (TW3) to ensure that the young person met the maturity criteria.

Discussions took place between PS and LR and the wider team (NPW/JKW and RJC) to confirm medical eligibility and ability to engage with the lifestyle and exercise intervention package.

The families were contacted 1 -7 days after the initial meeting to find out if they were keen to take part. If agreeable, arrangements were made to attend for the formal consent process and pre balloon assessments.

Written consent was obtained (in triplicate-one for the family, one for the case notes and one for the site file) from all the study participants and their parents.

#### Patient confidentiality

All subjects were given a patient number in the order in which they were recruited to the study (BOB01 to BOB12) and only the principal investigator was aware of the identity.

### Medical contacts and lifestyle intervention package

Each young person after recruitment came in for a day of medical tests before balloon insertion. These included anthropometric measurements (weight/height/waist and hip circumference), Blood Pressure, Blood tests, OGTT (oral glucose tolerance test), DEXA and HRpQCT scans.

The balloon was inserted a few days later and stayed in for 6 months. The plan was for the young person to be seen weekly for the first 4 weeks by PS (PI for the project/ PhD student) and then monthly till balloon removal at 6 months.

Further medical review of the young people, BP, anthropometric measurements took place at 12 and 18 months.

The same detailed blood tests and scans were repeated within 2-3 weeks of balloon removal (at 6 months) and then again at 24 months follow up.

The exercise and science officer at Sheffield Hallam University (LR) lead the lifestyle and exercise intervention. An overview of the programme is provided below in Figure 10.

Figure 11 - Exercise protocol overview



Weekly visits for 4 weeks before the balloon insertion, 26 weeks while the balloon was insitu and for 8 weeks after the balloon was removed

Exercise therapy sessions were planned once a week on a 1:1 basis or a small group basis (max 3) dependent on geographical spread of participants (with emphasis on sessions being delivered locally). Each session lasted an hour during which individuals undertook 30 minutes of integrated exercise consisting of four-minute bouts of moderate intensity exercise with two-minute rests between each bout. Mini games were also included to promote a fun element and introduce a self-referenced competitive element into the sessions.

During initial blocks “Life before the balloon” and “living with the balloon” the focus was on cognitively based intervention strategies such as consciousness raising and cognitive reappraisal. In the latter blocks more behavioural based interventions were introduced for example goal setting, self-monitoring and finding social support. Dietary advice and modification to maintain a healthy diet for the initial 6 months was offered initially (2 sessions 1 hour each) and reinforced at each contact to encourage caloric restriction.

A flow chart to explain how the visits were organized and what would be done at each visit is provided below.

Figure 12 - Flow chart of protocol overview

**Baseline Assessment - Intragastric balloon inserted Endoscopically**

Auxology - Height, weight, BMI, Waist: hip ratio, Blood pressure

* OGTT & Incretins, lipids, U&E’s, LFT’s, Adipokines, Bone profile and turnover markers, Vitamin A,D & E levels
* DEXA scan assessment of fat mass & bone density, HRpQCT for bone architecture
* Assessment physical fitness & activity. Modified Balke exercise protocol and PAQ Adolescents
* Questionnaires: CY-PSPP, PedsQL, Theory of Planned Behaviour

**Balloon – in situ for 6 months.**

**Weekly lifestyle exercise**

**package and monthly home visit by the exercise science officer**

U&E’s weekly for 4 weeks

Height, Weight & BMI monthly

**6 months – Intragastric balloon removed Endoscopically- 6 month**

* Auxology - Height, weight, BMI, Waist: hip ratio, Blood pressure
* OGTT & Incretins, lipids, U&E’s, LFT’s, Adipokines, Bone profile and turnover markers , Vitamin A,D & E levels
* DEXA scan assessment of fat mass & bone density, HRpQCT for bone architecture
* Assessment physical fitness & activity. Modified Balke exercise protocol and PAQ Adolescents
* Questionnaires: CY-PSPP, PedsQL, Theory of Planned Behaviour

**12 months – 6 months post balloon removal**

* Height, weight, BMI waist: hip ratio, blood pressure
* Questionnaires: CY-PSPP, PedsQL, Theory of Planned behaviour
* Assessment physical fitness & activity. Modified Balke exercise protocol and PAQ Adolescents

**18 months follow up**

**18 months - 12 months post balloon removal**

* Height, weight, BMI, Waist: hip ratio, Blood pressure
* Questionnaires: CY-PSPP, PedsQL, Theory of Planned Behaviour
* Assessment physical fitness & activity. Modified Balke exercise protocol and PAQ Adolescents

**24 months – 18 months post balloon removal**

* Auxology - Height, weight, BMI, Waist: hip ratio, Blood pressure
* OGTT & Incretins, lipids, U&E’s, LFT’s, Adipokines, Bone profile and turnover markers, Vitamin A,D & E levels
* DXA scan assessment of fat mass & bone density, HRpQCT for bone architecture
* Assessment physical fitness & activity. Modified Balke exercise protocol and PAQ Adolescents
* Questionnaires: CY-PSPP, PedsQL, Theory of Planned Behaviour

### Day 1

Instructions regarding OGTT were given by phone and email to ensure that the young person was fasted from the night before.

Consent was taken and documented in source file on the morning of the tests.

### Anthropometry

**Height measurement:** Height was measured using a stadiometer (SECATM 214 portable stadiometer, Birmingham, UK) to the nearest completed 0. 1 cm. Before they were measured, participants had to remove their shoes, heavy outer garments, and hair ornaments that could lead to falsely elevated height.

The participant was then asked to stand so that their back was against the stadiometer with the back of the head, back, buttocks, calves and heels touching it all through with the feet together.

The head was positioned with the top of the external auditory meatii level with the inferior margin of the bony orbit which is known as the Frankfurt Plane. The headpiece of the stadiometer was then brought down to touch the participants head whilst flattening the hair.

Gentle pressure was applied to the mastoid process to ensure the head was in the correct plane and height was then recorded.

**Weight measurement:** Weight of subjects was also measured to the nearest 0. 1 kilogram (kg). The patients were weighed in their light inner clothing with shoes removed using a calibrated electronic balance scales (SECATM 770 digital weighing scales, Birmingham, UK).

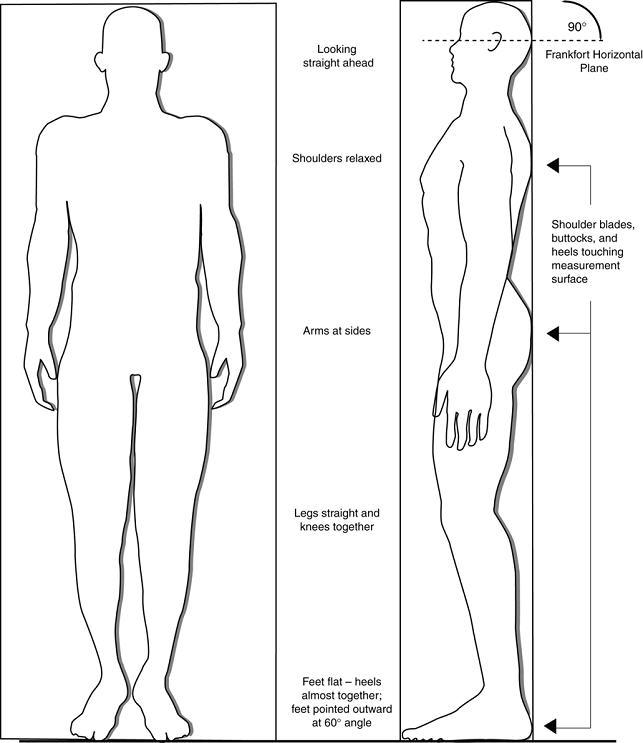
**BMI Calculation:** BMI was calculated from the values derived from height and weight measurement using the formula:

Body Mass Index (kg/m2) = Weight (kg) divided by Height2 (m2)

The Child Growth foundation charts and a Microsoft Excel® programme used to work out the BMI SDS based upon the data from the UK have been used in this study to define grades of obesity according to BMI SDS (The Child Growth Foundation, London, United Kingdom).

The positioning for height measurement explained in Figure 12 . The back of the head, back, buttocks, calves and heels should touch the back of the stadiometer and feet together. (Taken from Phenxtoolkit.org.)

Figure 13 - Position for Height measurement



**Waist circumference:** Participants were asked to stand with their feet close together with their weight equally distributed to each leg. Measurements were taken with a SECATM 200 waist circumference measure (Birmingham, United Kingdom) which measures from 15-200 cm with 1 mm graduations.

Waist circumference was measured between the 10th rib and top of the iliac crest (sensitive and specific for visceral obesity as per WHO guidelines). Participants were asked to breathe normally and the measurement was taken at the end of gentle exhalation to prevent subjects from holding their breath. Measurements were made to the nearest 0.1 cm.

Figure 14 - Waist circumference measurement



**Hip Circumference:** Hip circumference was measured around the widest portion of the buttocks with the tape parallel to the floor. The individual was asked to stand with feet close together, arms at the side with measurements taken at the end of normal expiration.

Each measurement was repeated three times and an average calculated.

The World Health Organization (WHO) use WHR (waist to hip ratio) as an indicator of abdominal obesity (>0. 90 for males and >0. 85 for females) (251)

Several studies have shown that waist circumference and waist to hip ratio are better discriminators of cardiovascular risk factors than BMI in adults(252).

Both waist circumference and waist to hip ratio are related to increased risk of all-cause mortality throughout the range of adult BMI (253).

In Taylor’s study of 580 children (302 boys) aged 3-19 years, waist circumference did better than waist hip ratio to measure truncal adiposity as assessed by DXA. (254)

We already know that abnormalities in lipid and insulin concentrations correlate to waist circumference in young people (255). In our study, we measured hip and waist circumference at baseline, at 6 months after balloon removal, 12, 18 and 24 months.

Tanner Staging

Girls were asked timing of menarche and boys were asked to self-assess puberty looking at a pen picture. (AppendIx 9)

Skeletal maturity was assessed by using the Tanner-Whitehouse 3 (TW3) method for some of the young people for confirmation. This was performed by the Growth nurse alone to avoid possible variability between raters.

**Urine tests:** Urine pregnancy test was performed on all the girls as per guidance from the radiation expert at Sheffield Teaching Hospitals NHS Foundation Trust to ensure that it was safe for the girls to be exposed to ionising radiation.

A urine sample was also collected to measure levels of carboxyterminal cross linking telopeptide (CTx) which is a marker for bone resorption. Osteoclasts will generate CTx and NTx when in apposition with the bone surface, as a breakdown product of bone resorption and we wanted to see if this changes with weight loss(256).

#### Collection of blood samples

A cannula was inserted and bloods taken by PS or the nurses at the Clinical research facility.

113 ml of Polycal was mixed with an equivalent amount of water and administered to the young person (1. 75gm/kg glucose is the dose for an OGTT with a maximum of 75 grams of anhydrous glucose which is contained in 113 ml of polycal). All young people received 75 g due to their body weight.

The following tests were taken in the young people at visit 1 and repeated at balloon removal at 6 months and then at 18 months follow up.

* Full Blood count
* U&E, Liver function and Bone profile including alkaline phosphatase
* Vitamin A, D &E
* HBA1c
* T4, TSH
* Lipid profile
* Bloods collected at 0,30,60,90 and 120 minutes for glucose, insulin, GLP-1 and GIP during the OGTT

Send away samples included the following:

* Adiponectin, leptin
* Ghrelin
* Bone resorption markers- Urine CTx and urine NTx
* Bone formation markers – serum Osteocalcin and P1NP
* Osteokines- serum OPG (Osteoprotegerin), DKK-1 (Dickkopf-1) and RANK-L (Rank-Ligand)
* Incretins-GLP-1 (Glucagon like peptide-1) and GIP (Gastric inhibitory peptide)

#### Sample preparation - Centrifuge and storage

* 20 ml of blood was taken from each participant initially at 0 minutes.
* 5 ml of blood from this was taken into a plain vial and allowed to clot for 30 minutes. It was then spun in refrigerated centrifuge for 15 minutes at 3000 revolutions per minute (Hettich Universal 320R (serial number 4751)) as per advice from the biochemist.
* Supernatant was then aliquoted into 2 plain tubes marked A and B and frozen at -80 degrees. This was for measurement of the osteocalcin, osteokines, leptin and adiponectin.
* 2 ml of blood was taken into a plain vial containing 20 microlitres of PEFABLOC for the ghrelin measurement. This was also allowed to clot for 30 minutes and then spun for 15 minutes at 3000 rpm. Supernatant was then removed into 2 plain tubes marked G/A and G/B and frozen at -80 degrees.
* 4 ml of blood was added to an ice cooled EDTA bottle containing 40 microlitres of DPP-IV.
* This was spin at 4 degrees at 10 minutes @ 2000 revolutions.
* Serum was then taken of in 2 bottles and frozen at -80.
* This was used for measuring the incretins, GLP-1 and GIP.
* Further 5. 5 ml of blood were taken at 30,60,90 and 120 minutes for incretins (GLP-1 and GIP) and glucose and insulin
* Samples were stored within 30 minutes of centrifugation. Any freeze thaw cycle that a sample underwent was documented.
* All urine samples for Ctx and Ntx were collected in a universal container and stored at -20 degrees.

#### Sample analysis

All samples other than the send away were analysed at SCH (Sheffield Children’s Hospital) and RHH (Royal Hallamshire Hospital) (described in Table 3

Send away samples are described in Table 4.

Table - Blood tests, methods, analyser used with sensitivity and precision

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **TEST** | **ANALYSER** | **METHOD** | **SENSITIVITY** | **PRECISION** | **COMMENT** |
| Insulin | Cobas 602  Module  (Roche) | Immunoassay | Analytical sensitivity 1. 39 pmol/L (lower detection limit) | Within-Run CV 0. 7 to 1. 5% mean 1%, Total CV 2. 4-4. 9% mean 3. 6% | Roche assay insert |
| Na, K, Cl, Urea,  Total Bili, Conjugated Bili, Total Glucose, Protein, ALP,  AST, ALT, GGT  Calcium, Albumin, Phosphate  Lipid Profile (Chol, Trig, HDL, LDL) | Vitros 5,1 FS  System  (Ortho Clinical  Diagnostics) | Micro Slide Technology  Potentiometric (direct ISE)for Na, K & Cl; Colorimetric/Rate using Reflectance  Spectrophotometry all other tests |  |  | Check website for Vitros 5,1 FS Ortho Clinical Diagnostics |
| TFT (TSH & FT4 | Architect  *i* 1000  System  (Abbot) | Immunoassay  (Chemiluminescent  Microparticle Immunoassay) | FT4 analytical sensitivity (limit of detection) 3. 6 pmol/L  TSH analytical sensitivity ≤ 0. 0025 mIU/L | FT4 precision ≤ 10% Total CV 5. 27%, Within-Run CV 3. 2%  TSH precision ≤ 10% Total CV 2. 47%, Within- Run CV 1. 75% | Taken from Abbott assay insert |
| HbA1C | DCA Vantage  (Siemens) | Immunoassay  (Inhibition of Latex Agglutination) | Analytical sensitivity  4 mmol/mol (low)  130 mmol/mol (high) | Within-Run CV  2. 2-3. 7 %  Between-run CV  0. 9-4. 3% | DCA System insert |
| Vitamin D | Acquity Ultra Performance LC/Quattro MS  (Waters) | UPLC/Mass Spectrometer  Semi-automated hexane extraction | Lower limit of detection 25-OH Vitamin D2: 6nmol/L  VitaminD3: 3. 5nmol/L | D2: With-in Run CV 4. 4-6. 7%,Total CV 5. 2-6. 4%  D3: With-in Run CV 4. 3-4. 5%, Total CV 5-6. 2% |  |
| Vitamin A & E |  | HPLC |  |  |  |
| FBC | ADVIA 120  ADVIA 2120  (Siemens Healthcare Diagnostics | ADVIA Haematology  System  (Automated and manual CBC, RBC, Differentials) |  |  |  |

Table - Send away samples

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sample** | **Aliquot Size (microliters)** | **Number of Aliquots** | **Total amount of serum (microliters)** | **Sent to** |
| Adiponectin | 200 | 2 | 400 | Jenny Jones (London) |
| Leptin | 200 | 2 | 400 | As above |
| RANK-L | 200 | 2 | 400 | As above |
| OPG | 200 | 2 | 400 | As above |
| DKK-1 | 200 | 2 | 400 | As above |
| Osteocalcin | 200 | 2 | 400 | As above |
| P1NP | 200 | 2 | 400 | As above |
| Ghrelin | 500 | 2 | 1000 | As above |
| GLP-1 | 500 | 2 | 1000 | As above |
| GIP | 500 | 2 | 1000 | As above |

Analysis of send away samples were carried out by:

Mrs J Jones, Senior Biochemist

Centre of Obesity, Dept of Medicine UC

The Rayne Building

5 University Street

London

WC1E 6JJ

**Information on all assays:**

* Leptin was assayed by Elisa from Millipore with a sensitivity of 0. 78 ng/ml (Intra assay CV  4. 6% @ 2. 3 ng/ml and Inter assay CV  6. 2% @ 2. 3 ng/ml).
* Ghrelin was assayed by Elisa from Millipore with a sensitivity of 50 pg/ml (Intra assay CV 1. 2% @ 384 pg/ml Inter assay CV  7. 8% @ 384 pg/ml).
* Total Gastric Inhibitory Polypetptide (GIP) was measured by sandwich ELISA with a sensitivity of 4. 2 pg/ml (Intra-assay variation 6. 7% @ 15 pg/ml, Inter-assay variation 6. 1% @ 26 pg/ml).
* Glucagon like Peptide -1 (GLP-1) assayed bytwo-site sandwich ELISA with a sensitivity of 0. 6 pmol/L. (Intra-assay variation 3. 7% @ 3. 0 pmol/L and Inter-assay variation 6. 2% @ 4. 1 pmol/L).
* Adiponectin assayed by sandwich ELISA with a sensitivity of 0. 2 ng/ml. (Intra-assay variation 7. 4% @ 17. 7 ng/ml, Inter-assay variation 8. 4% @ 17. 7 ng/ml)
* Serum was analysed for the bone formation markers procollagen type I amino propeptide [P1NP] (Orion Diagnostica, UniQTM P1NP RIA, Oulunsalo, Finland)
* Urine for carboxy-terminal telopeptide of type I collagen [CTX] (Urine CrossLaps® EIA, Immunodiagnostic systems, Beckmen Coulter, California, USA)
* Serum was analysed for osteoprotegerin [OPG] (Osteopro-tegerin ELISA FS-01F1, Immunodiagnostic Systems Ltd®. Newcastle, United Kingdom)
* Receptor Activator of Nuclear κB ligand [RANKL] (sRANKL ELISA, Biomedica®, Vienna, Austria)
* Adiponectin (Human Adiponectin/Acrp30 Immunoassay, Quantikine®, R&D systems, USA)
* Leptin (DSL Active Human Leptin ELISA; Webster TX, USA)
* Wnt-signalling inhibitor, Dickkopf-1 [DKK1] measured by ELISA

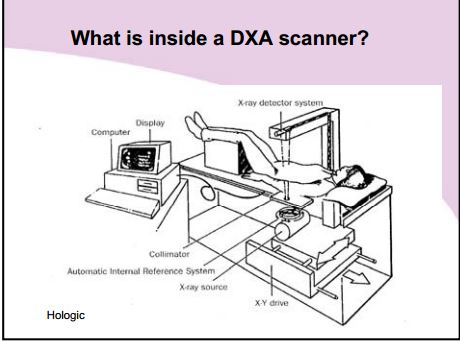
#### Scans - DXA

Patients then went to the X-ray department at the children’s hospital for a dual energy x-ray absorptiometry scan (DXA) whole body and lumbar spine.

Principle: Several types of DXA are available but the principle is essentially similar. A radiation source is aimed at a radiation detector that is placed opposite the site to be measured. The patient is then placed on a table in the path of the radiation beam (Dual energy beam is produced by using a metal filter in the beam to split the spectrum into high and low energy parts in the Lunar systems). The source/detector assembly is then scanned across the measurement region and the attenuation of the radiation beam is determined which relates to the bone mineral density (BMD)(257, 258).

Figure 15 showing what was inside the original DEXA scanner is shown below.

Figure 15 - Principles of a DXA scanner



For a given thickness, the attenuation increases with the density of the material.

BMD is the measured parameter and allows the calculation of the bone mineral content in grams using the 2-dimensional projected area in cm2 of the bone being measured.

In children and young people who have not yet attained peak bone mass, Z scores are used where the patient’s BMD is compared with age matched (gender and race matched) and expressed as a standard deviation score (SD)(259).

#### Scanning in Obese patients

There are several challenges in the scanning and analysis of obese patients. The weight restrictions of the scanner (the upper limit of the lunar iDEXA was 182 kg and the heaviest patient in the study was approximately 179 kg) were not an issue for us, however the table dimensions were an issue. Obese patients have a greater abdominal thickness and more x-rays are attenuated by fat. This leads to grainy images due to high degree of attenuation which the iDXA cannot compensate for completely. However, the GE Lunar system automatically alerts the user to the need for the ‘thick’ scan mode if the patients’ weight exceeds a particular level.

The correct positioning for lumbar spine involves a patient straight on the table parallel to the scanner bed (spine should be straight in the image), not rotated (spinous processes are centered) and centered in the field with equal amounts of soft tissue on either side. Legs should be raised and placed on a positioning block with their knees at about 90 degrees (See figure 16). However, for our young people with relatively minimal musculoskeletal issues, this was not necessary.

Figure 16 - Position for lumbar spine DXA

.  brochure idxa 16 bl.indd

For a total body scan, it is essential that the patient lie supine and the whole body including the arms be included in the scanning field.

Figure 17 - Positioning for Total Body DXA

 medicalexpo.com

In our study, some of the patients were too wide for the scanning field. Therefore, different standardized methods to deal with obese patients were utilized as outlined below.

The patients were moved such that they were off the centre line of the scan table to ensure that at least one side, typically the right side is completely included in the scan field, (hemiscan protocol); however there was no real difference when compared with keeping them in the middle that has also been seen in previous work(260). The other advocated method involves *Imputation of arms or* legs in which case, the patient is positioned off axis in such a way that the entire trunk is on the table but the left arm and leg are not scanned and right side values are used for the left as well. The equations for this are more complicated than the hemi scan method and it is assumed that the accuracy for both is similar.

Positioning was carefully documented using the protocol for the WB DXA acquisition and the radiographer ensured that the young person was in the same position for all 3 scans to ensure reproducibility. Initially the imputation method was used for our young people, however, later they were scanned with all patients in the centre of the table. However, to maintain consistency if the imputation method was used in first scan, this was used in the follow up scans as well.

Three trained radiographers at Sheffield Children’s Hospital performed total body and lumbar DXA scans. Subjects wore underwear with a light gown or light clothing for the scan. They were asked to remove any objects including jewellery and hair accessories and clothing containing metal on the basis that metal can potentially attenuate the x-ray beam. All females of reproductive age were questioned regarding pregnancy. All females had to undergo pregnancy testing. The young people were asked to remain still during the procedure to avoid movement artefact. The young people were positioned according to the region analysed. The regions of interest (ROI’s) measured by total body DXA are upper limbs, lower limbs, head (not analysed), ribs, pelvis and spine.

**Lumbar spine DXA measurements:** Subjects were positioned supine in the midline of the scanning field. The scan commenced at lumbar vertebrae 5 (L5), which is approximately at the level of the umbilicus. On commencing the scan, the beam travels in a foot to head direction. The scan image appears on screen. The beam is discontinued when it reaches the T12 thoracic vertebra that approximates to the lowest ribs to be sure of the vertebral segmentation. The region of interest in this study was the L1-L4 vertebrae. The ROI demarcating lines were placed in the intervertebral space below T12 caudally, and in the midline of the intervertebral space between L5 and S1 distally. Bone measures were derived from scanning measurements of L1 to L5 vertebrae. The DXA scanner then derived measurements for each individual lumbar vertebra and then a combination of adjacent vertebrae between L1 and L5.

The lunar iDXATM we used for our study performs a 6-point calibration with normal, osteoporotic, osteopenic BMD values as well as lean, normal and obese values, which makes it more precise and accurate than previous systems. The basis of this is the Performa X-Ray Tube which delivers X-ray flux to measure and image patients up to 182 kg but still provides a low dose performance.

Total scan time was about 4-5 minutes (but with positioning took about 15 minutes)with typical scan exposure of 149 microGy each time, total of 447 over the 3 visits as per the manufacturers standard and recommended scan acquisition protocols

Outputs include BMD of the lumbar spine with age matched percentage and z score, as well as BMC (gms), BA (cm2), width and height of the lumbar spine (cm).

Total body BMD along with z score as well as Total Body Less Head (TBLH) BMD with its z score were also measured. Total and TBLH BA and BMC were also calculated.

Initial total body bone measurements include head analysis. As the skull contributes to a significantly greater proportion of total body BMC in younger children, exclusion of skull BMC and BA provides a more accurate means of detecting changes in total body BMC and BMD (Taylor, Konrad et al. 1997).

Body composition data

* Total body fat mass (FM - grams)
* Total body lean mass (TLM - grams)
* Percentage total body fat mass (%FM)
* Truncal fat mass (TFM - grams)

TBLH BMD, BMC and BA as well as lumbar spine BMD, BA and BMC and TBLH fat and lean mass were compared at visits 0,6 and 24 months.

Quality assurance was carried out daily by scanning an aluminium phantom in the morning prior to subject measurement for scanning accuracy.

Figure 18 - QA block phantom for optimal calibration



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Size-related artefactual increase in aBMD with increasing height and weight is well recognised – however, we are dealing with individuals so far from the average size that it isn't clear that any of the multiple suggested adjustment processes would be applicable. We will also have the HRpQCT measures to help us understand at least the region-specific changes that are close to the sites that are most often fractured in children and obese individuals.

#### HRpQCT

Patients then went to the NIHR Clinical Research Facility (CRF) at Northern General Hospital for a High-resolution peripheral quantitative computed tomography (HRpQCT) scan of the distal radius and tibia.

**Scanning:** Though measurement of areal BMD (aBMD) by DXA is used as a standard to predict fracture risk, many fractures do occur in individuals with normal BMD. The ability of a bone to sustain a certain load without fracturing depends on the amount of bone (bone mass), the bone morphology (microarchitecture) and the inherent properties of the bone tissue. Recent advances in high-resolution imaging allow us to quantify cortical and trabecular structures in vivo at the distal radius and tibia with a voxel size of 82 microns(246). `

The scanner used is the XtremeCT (Scanco Medical AG, Brüttisellen, Switzerland). The non-dominant, non-fractured side was measured. If there was patient movement, a single repeat scan was acquired

The arm or leg of the patient was immobilized during the examination in an anatomically formed carbon fibre shell. Each participant was positioned as per the manufacturer protocol by the same manufacturer trained technician.

All participants were scanned at the distal radius and tibia using the manufacturer’s standard in vivo protocol as previously described (261-263), resulting in a 2. 8 min scan (source potential of 60 kVp, tube current of 1000 microA, 100 ms integration time). An antero-posterior scout view was used to define the measurement region. If the growth plate was visible, the images were obtained from 1mm proximal to the proximal limit of the growth plate.

Each measurement included 110 image slices corresponding to a 9. 02 mm length of the forearm/leg at an isotropic voxel size of 82 microns. If the growth plate was visible, the first image slice was 9. 5 mm and 22. 5 mm proximal to the reference line for the distal radius and distal tibia respectively. The effective ionising radiation dose to the participant was approximately 3 microSv per measurement. In comparison to this, the radiation exposure due a chest X- ray wold be 20 microSv.

A single operator (dual) assessed the quality of the images visually as perfect (G1) or slight (G2) or moderate (G3) or unacceptable (G4) movement artefact with G4 images excluded from the study(264).

The HR-pQCT image segmentation and analysis were done using standard built in software (version 6. 0, Scanco Medical).

**HRpQCT registration technique for longitudinal measurements**

There is a a two-dimensional method using the Cross-sectional area (CSA) based registration which is the standard registration process for the machine. This automatically matches the bone area on a slice by slice basis and can convert the stack of slices in such a way that the best possible overlap is provided and the common volume determined. This information is automatically added to the HRpQCT measurements that are obtained from the XtremeCT workstation.

The built in 2-D registration method described above can deal with slice shifts i.e. the follow-up measurement slice stack is more distal or more proximal to the baseline measurement.  However, this approach does not handle any rotations in the follow-up slice stacks i.e.the arm is slightly rotated compared to baseline.  Researchers have been trying to develop 3-D registration methods (including the team at Northern General) but these are much more complex and have not been incorporated into the XtremeCT software yet.

The measurements shown in Table 6 and 7 were recorded. These were taken for both the radius and the tibia at 3-time points-0, 6 and 24 months.

Extended cortical bone analysis was carried out using the methods described by Burghardt to clearly identify the periosteal and endosteal boundaries of the distal radius and tibia and detect intracortical pore space morphologically consistent with Haversian canals(265). This allowed the assessment of cortical microstructural properties such as cortical thickness (Ct.Th, mm), the cortical tissue mineral density(TMD,mgHA/cm3) as well as cortical porosity(Ct.Po,%).

Essentially, in the first stage, the cortical bone compartment is segmented by an autocontouring process which includes the extraction of the periosteal surface. The endosteal boundary is detected next which defines the trabecular compartment. The periosteal and endosteal aregions are then subtracted to get the apparent cortical compartment from which the mineralized section is obtained by masking the bone structure.

The second stage involves intra-cortical porosity segmentation which is carried out as follws: a) firstly extracting pores fully surrounded by bone, b) then extracting any connected pores not fully surrounded by bone c) filling the binary cortex with all found pores and using 2D connectivity to etract any remaining pores and finally d) combining all pores into a final picture to assess the pore diameter and pore diameter sds. The final stage involves combining the first 2 stages to refine the cortical area of interest.

The process can be quite complicated depending on whether the cortex is thick or porous as the accuracy of these calculations is based on how the boundary is defined.(266)

Table 5 - HRpQCT measurements

|  |  |  |  |
| --- | --- | --- | --- |
| **Densitometric measurements** | **Microstructural measurements** | **Cortical measurements** | **Strength parameters** |
| Total density  (Dtot, mg per cubic cm) | Trabecular number  (Tb.N,mm) | Cortical porosity  (Ct. Po, percent) | Stiffness (kilonewtons/mm) |
| Trabecular density  ( Dtrab, mg per cubic cm) | Trabecular thickness  (Tb.Th, mm) | Cortical pore diameter (Ct.Po.Dm, micrometer) | Estimated Failure Load (kilonewtons) |
| Cortical density  (Dcort, mg per cubic cm) | Trabecular separation  (Tb.Sp, mm | Cortical tissue mineral density (TMD, gms per cubic cm) | % load carried by the trabecular bone (distal) |
|  | Bone volume fraction  (BV/TV, percent) |  | %load carried by the trabecular bone (proximal) |
|  | Cortical thickness  (Ct.Th, mm) |  |  |

Table 6 – HRpQCT measurements-definitions

|  |  |
| --- | --- |
| **Total Area (Tt. Ar mm2)** | Total area; the average cross sectional area of the whole bone circumscribed by the endosteal contour |
| **Cortical Area (Ct.Ar mm2)** | Cortical area; the average cross sectional area of the cortical compartment between the periosteal and endosteal contours |
| **Trabecular Area (Tb.Ar mm2)** | Trabecular area; the average cross sectional area of the trabecular compartment circumscribed by the endosteal contour |
| **Cortical BMD (mg HA/cm3)** | Cortical bone mineral density; mean mineralization of the cortical volume of interest |
| **Cortical TMD (mgHA/cm3)** | Mean mineralization of the segmented cortical bone voxels after surface partial volume suppression |
| **Cortical Thickness (Ct.Th, mm)** | Apparent cortical thickness; mean 3D distance from periosteal boundary to endosteal boundary disregarding intracortical pores |
| **Cortical Porosity (Ct.Po %)** | Relative voxel based measure of the intracortical pore space normalized by the sum of the pore and cortical bone volume |
| **Cortical Pore Diameter (micrometers Ct.Po.Dm)** | Mean 3D diameter of the intracortical pore space |
| **Ct.TV (mm3)** | Cortical total volume: the volume of all voxels contained within the cortical volume of interest |
| **Ct.BV (mm3)** | Cortical bone volume: the volume of all bone voxelswithin the cortical volume of interest |
| **BV/TVd** | Ratio between bone volume and total volume of tissue (Derived bone volume fraction) |
| **Tb.N** | Mean number of trabeculae |
| **Tb.Thd** | Mean thickness of trabeculae (Derived) |
| **Tb.Spd** | Mean space between trabeculae (Derived) |

**Finite element analysis:** HR-pQCT also offers new ways of predicting bone strength by using finite element analysis (FE) which is obtained directly from segmented HRpQCT images(261) using software developed by Scanco medical. FE analysis uses a complex system of points (nodes) with each ‘node’ joined to other nodes using ‘mesh elements’. A ‘mesh’ or web is created which is programmed to contain material and structural properties which would decide how a structure would behave under stress.

Compression and other mechanical tests can be simulated on scanned bone segments to determine Stiffness, Strength of bone and Tissue loading level.

This is fully automated and validated for the assessment of in vivo bone strength. A compression test can be run to simulate a fall from standing height on to an out-stretched hand – for example to mimic the trauma associated with a Colles fracture. Applying a load in a longitudinal direction at one end of the bone while the other end of the bone is constrained simulates the fall. Failure of the bone is said to occur when greater than 2% of the bone tissue is strained beyond a critical level of 3500 strain. Similar models were used when examining the radius and tibia(263). The Bone research unit at the Northern is the only centre in the UK using the FE software provided by Scanco Medical.

Other FEA-derived variables used in our analyses included the following: stiffness (kilonewtons/mm), ultimate failure load (kilonewtons), the percentage of load carried by the trabecular bone at the distal and proximal surface of the volume of interest (% load trab distal and % load trab proximal, respectively), the percentage of load carried by the cortical bone at the distal and proximal (%cortical distal load and %cortical proximal load) surfaces of the volume of interest (VOI)

The stability of the Xtreme CT was monitored by daily measurements using a manufacturer device-specific phantom (Scanco Medical) with weekly monitoring for the microstructural properties of bone.

**Questionnaires and Treadmill test at Sheffield Hallam University**

Participants then went to Sheffield Hallam University to complete a treadmill test and QoL questionnaires with the exercise and science officer LR.

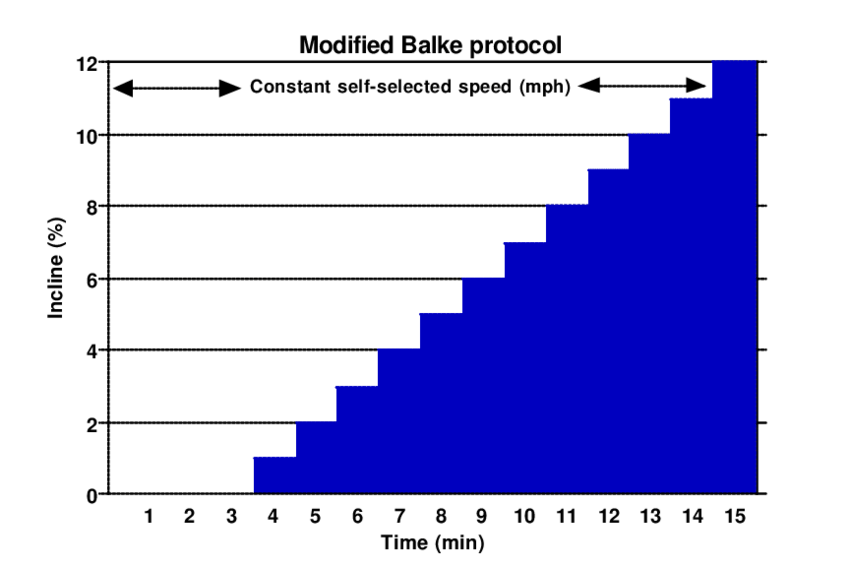
Three different questionnaires were used: (appendix 11)

1. Self-perception was measured on the subscale from **the Children and Youth Physical Self-perception Profile (CY-PSPP) developed in 1989 and adapted for use in children in 1995.** This contains 6 subscales; Sport/Athletic, Attractive Body Adequacy, Condition, and Strength competence as well as Physical and Global self worth. The Children and Youth Physical Self-perception Profile (CY-PSPP) assesses the degree to which young people view themselves as competent in a variety of physical domains(267).
2. **The PedsQL** Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents including 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). The PedsQL consists of brief, practical, generic core scales suitable for use with healthy school and community populations, as well as with paediatric populations with acute and chronic health conditions (268). In a study looking at health related Quality of Life, overweight and obese adolescents reported significantly lower scores compared to their healthy counterparts(269).
3. **Assessment of planned behavior** The Theory of Planned Behaviour (TPB) was developed to predict behaviours in which individuals have incomplete volitional control(270). In light of the fact that the lifestyle intervention study holds a focus on improving physical self-competence and self-efficacy towards exercise and given that perception of behavioural control as indicated by TPB can reflect past experiences, anticipation of upcoming circumstances, and the attitudes of the influential norms that surround the individual, components from the TPB were assessed(271). Participants were asked to indicate by circling a number between one (strongly agree) and 7 (strongly disagree) to what extent they agree with statements such as; "I would like to participate in physical activity at least three times per week", "If I wanted to, I could easily take part in regular physical exercise" or "Most people who are important to me, think I should take part in regular physical exercise".

**Physical fitness and physical activity was measured using the modified Balke protocol**

The modified Balke protocol (depicted in figure 18) requires participants to walk at a pace of 1. 34 m s-1 at a grade of 6% for 2 minutes. At the end of the two-minute stage, the grade is increased by 2%. This continues until volitional exhaustion. On the occasions that the treadmill reaches maximal elevation the participant continues to walk at that gradient until volitional exhaustion. The speed of the treadmill remains constant at 1. 34 m s-1 for the duration of the protocol. The protocol ends at volitional exhaustion. The test is continuous with no rest periods between each stage. Heart rate (HR) was measured during the last minute of each stage using a short-range radio-telemetry monitor.

Figure 19 - Depiction of the modified Balke protocol



https://www.researchgate.net/profile/Robert\_Robergs/publication/228596508/figure/fig1/AS:637688130596873@1529048106428/Modified-Balke-treadmill-VO-2-max-protocol.png

The young people also completed the **Physical Activity Questionnaire** for Adolescents(272, 273).

These were repeated at 6 months after balloon removal, at 12 months, 18 months and then 24 months (18 months post balloon removal).

### Stage 2 (over next 2-3 weeks)

#### Dietetic session

This was conducted either by phone, face to face or skype with LD, Specialist dietician with expertise in bariatric surgery. Current diet, portion sizes was discussed and food dairies examined. Advice re healthy eating, portion control and reading labels was provided and reiterated on a regular basis, though calorie restriction was not emphasized.

Dietetic booklet to prepare for balloon insertion was given and plan for the 2 weeks after insertion explained as the young person moved from a liquid to semi solid to a normal diet.

#### Lifestyle intervention-life before the balloon

Weeks 1-4 included weekly sessions at Hallam University with LR to introduce the programme, and outline what would happen for the children and their families. Discussion centered on motivation, life-style activity, what is achievable and how much the young person was willing to do to lose weight. The scene was set for the journey ahead with a pledge tree that had the goals for the first few weeks and to plan life with the balloon in situ.

### Balloon insertion

Pathway followed is described below:

PS liaised with MAT (paediatric gastroenterologist) regarding his availability, as well as with the gastroenterology secretaries and clerk in appointments to confirm date for procedure. Friday mornings were considered best in view of the endoscopy list and theatre commitments as well as having minimal impact on school attendance. A hospital letter regarding admission procedure were sent as usual hospital policy 2-4 weeks prior to the date of the procedure.

Dietetic information was reiterated one week earlier and a phone call was made by PS to speak to families 48-hour prior to admission to the hospital. Plans for the day of balloon insertion were clarified and dietetic restrictions from 24 hours prior to balloon insertion reiterated.

GPs were sent a letter explaining the BOB Study, the rationale for the project, the possible complications and side –effects that required monitoring along with a request to prescribe PPI’s (proton pump inhibitors) for 6 months while the balloon was in situ.

Parents were also given a copy of the letter.

**Pre-theatre assessment and Consent:** Patients were admitted on ward M2 (gastroenterology ward) at 8 am on the day of the procedure and reviewed by PS.

The gastroenterologist and anesthetist took consent for the procedure.

**Procedure:** BIB insertion was carried out under general anaesthetic after endoscopy by a paediatric gastroenterologist. The balloon was put in the stomach and inflated under direct vision with normal saline stained with methylene blue so that patients were aware if early deflation occurred. The filling volume was kept at 500 ml (400-700 ml is quoted in the product literature) for all 12-young people after discussion and advice from the local adult bariatric surgeon. Some other adolescent studies have used 600-700 ml filling volumes, though no difference has been seen in the weight loss based on filling volumes.

IV Fluids and ondansetron/cyclizine and Dexamethasone were prescribed to reduce incidence of vomiting, a known complication post balloon insertion.

(Ondansetron 4mg three times a day (Intravenously (IV) followed by a liquid preparation), Cyclizine 50 mg three times a day (IV followed by water soluble tablets), Dexamethasone 8 mg one dose IV).

This was followed by regular ondansetron and cyclizine three times a day IV for 24 hours and Buscopan 20 mg IV four times a day to help with pain.

Patients were usually first on the list, therefore in theatres by 9am in the morning with the intra-gastric balloons inserted by mid morning.

**Progress in hospital:** The patients were observed on the Recovery ward till 1 pm approximately.

This was followed by transfer to Ward/HDU (Patient with OSA/if there were any complication) by 2 pm. Further reviews took place on the ward in the late afternoon. IV fluids were prescribed to gradually reduce to half by evening and then stopped by the following morning as the patient improved their oral intake.

**Discharge planning:** To ensure a smooth discharge process, TTO (to take out) plans were prepared for medications which included buscopan, ondansetron, cyclizine, multivitamin and PPI (30 mg lansoprazole fast tabs twice a day doses) for patients the same evening.

Electrolytes were checked as per protocol over the weekend due to the likelihood of persistent vomiting and risk of dehydration.

Plans were also made for weekly U&E and times and dates were finalized for the next 4 appointments.

PS then handed over plans for these patients to the weekend medical and nursing team. Phone contact was also maintained with the ward over the weekend followed by phone calls at home on alternate days by PS.

Face to face medical review was arranged for one week later.

### Life with the balloon

PS had weekly contact (sometimes daily over the phone) with patients for the first 4 weeks. Patients were reviewed on the research unit for monitoring of electrolytes, medication, side effects, and anthropometric measurements.

Parents had access to a 24/7 phone number to call if worried. They also had a letter explaining the procedure undertaken, side effects expected and the incidence of rare complications in case they presented to their local A &E out of hours (appendix 7).

2. 10 Lifestyle intervention

Participants commenced the life style intervention programme by week 3-4 of the balloon being in situ depending on how the young person was doing.

As per protocol, after the first month, patients were seen monthly by PS (measurement of weight, height, BP, waist circumference, hip circumference) at the hospital and weekly by the exercise science officer at the gym in Hallamshire.

Living with the balloon involved sharing initial thoughts and experiences with the balloon. Goal setting was reviewed with what child/young people hoped to achieve at each time point and how they thought this would be achieved.

Weeks 16-24 were geared towards preparing for Life after the balloon with

ongoing behavioral support, family participation in physical activity and education around planning healthy meals, regular meal patterns, portion sizes, reading food labels, healthier cooking and eating out sensibly.

### Balloon removal

These were done as a day case-on a morning list followed by review in the afternoon and same day discharge if possible.

PS ensured booklet 2 with dietetic plan on how to plan for balloon removal was sent to families 3-4 weeks before intended removal. PPI and multivitamins were stopped 48 hours prior to the procedure.

Letter was sent to the GP explaining that balloon was coming out by PS with a copy to the parent.

Plan for balloon removal was for the patient to be NBM (Nil by mouth) for 12 hours prior to the procedure, except for water which could be taken till up to 2 hours earlier. No solids were to be taken in the previous 24 hours.

The patient was admitted to ward M2 (gastroenterology ward) at the children’s hospital at 8 am and reviewed by the medical team. A drug kardex for medication was completed and arrangements made for discharge with pain relief medication.

Buscopan and paracetamol (pain relief) were given in theatre prior to procedure. The intra-gastric balloon was removed by mid-morning under general anaesthetic and the patients usually recovered by mid day. They were observed on the ward till afternoon to ensure that they were tolerating sips of water. A light diet was advised for the next 24-48 hours. They were discharged later the same day with a follow up phone call the next day at home by PS.

Follow up was arranged with PS in 2 weeks for repeat testing.

### Lifestyle intervention-weeks 24-32

Preparing for Life ahead-involved providing consistent behavioral support, building up to balloon removal, getting the young people ready for what to expect after the balloon came out, discussing coping strategies, and anxiety management. Young people were expected to continue to attend a weekly structured physical activity session with the exercise science officer. Home visits were undertaken if the family consented. There was also a discussion about getting the young people to meet the others in the study but enthusiasm for this was muted.

### Post balloon testing

The post balloon testing was like the testing involved prior to the balloon insertion and involved anthropometric assessment (weight, height, waist and hip circumference), blood pressure, OGTT, blood tests for incretins, Adipokines, osteokines, and bone turnover markers followed by DEXA scan and HRpQCT scans.

The young people also repeated the treadmill test, and completed the Physical activity questionnaire,Qol, CY-PSPP and Assesment of planned behavior questionnaires.

### Life-style intervention continued-weeks 34-42

Relapse prevention continued for 8 weeks after balloon removal to provide support for maintenance of weight after the balloon. It involved giving consistent messages regarding physical activity and life-style support and discussing the progress made so far in terms of goals met, change in behaviours, and longer-term expectations.

### Twelve month follow up

The twelve-month follow up involved a visit both to the hospital to see the doctor as well as the exercise and science officer at Hallam University. Anthropometric measures (weight, height, waist and hip circumference) were repeated and blood pressure rechecked with an overview of general health and well being. The treadmill test along with the Physical activity questionnaire, QoL, CY-PSPP and Assesment of planned behavior questionnaires were also repeated.

### Eighteen month follow up.

The eighteen-month follow up was identical to the twelve -month visit and involved a visit both to the hospital to see the doctor as well as the exercise and science officer at Hallam university. Anthropometric measures (weight, height, waist and hip circumference) were repeated and blood pressure rechecked with an overview of general health and well-being. The treadmill test along with the Physical activity questionnaire, QoL, CY-PSPP and Assesment of planned behavior questionnaires were also repeated.

### Twenty-four month follow up

The twenty-four-month testing was similar to the testing involved prior and post to the balloon insertion and involved anthropometric assessment (weight, height, waist and hip circumference), Blood pressure, OGTT, other blood tests for incretins, Adipokines, osteokines, and bone turnover markers followed by DEXA scan and HRpQCT scans.

The young people also repeated the treadmill test, and completed the Physical activity questionnaire, Qol CY-PSPP and Assesment of planned behavior questionnaires.

### Statistical Analysis

Sample size calculation has previously been discussed. But to summarise, a sample size of 12 was selected as the optimal size for a feasibility study. This was chosen based on advice from the Research design service at ScHARR (School of Health and Applied Research)(250). Gain of precision for both cross over trial and parallel group trials or an increase of 1 in the degree of freedom seemed to show no change once 12 participants were crossed. It is important in a study of this sort (where there is limited evidence of the efficacy of the treatment modality in a particular patient group), that the requirements of getting data on potential outcomes is balanced with minimizing the numbers exposed to the intervention. Hence, the sample size of 12 was agreed.

The primary outcome was the the patient’s BMI SDS at six-months and 2 years. Values are shown as mean ± standard deviation. A paired t-test was used to compare change in BMI SDS across the cohort. A 95% confidence interval (CI) for the mean difference was calculated. Whilst this was a feasibility study and not powered to show a significant difference, given the magnitude of the anticipated change in BMI (Reduction in BMI of 5. 0mg/m2 – Standard deviation 3. 4 from the adolescent section of the Sallet review(84), it was thought that it maybe possible to yield a statistically significant result with 8 patients. (2(Zα + Z1-β)2× (SD)2 / (Effect size)2 tocalculatre sample size equates to 7.25 patients)

Secondary outcomes such as change in BP, Lipid profile, GLP-1 and GIP Levels, bone architecture, bone mass and density, fat mass, adipokines, osteokines, bone turnover markers and QoL scores were also compared using paired t-test. Values are shown as mean ± standard deviation. P value of ≤0.05 was considered significant.

We did not use ANOVA as we did not compare multiple means. This would be used only if we wanted to compare 3 or more means. Means were compared between visit 1-2 and visit 1-3 for which the the paired T test was used.

A more complicated analysis could be used to look at changes over time but this would be instead of the paired samples t-tests.

The associations between weight loss and HR-pQCT variables and measures of bone strength with body composition and biochemical measures were assessed by Pearson correlations with 95% confidence intervals by the statistician supporting the study. To test for normality, the data was visually inspected using a data scatter. As there were no significant outliers, correlation used was Pearson.

There were a lot of correlations calculated and we discussed with the statistician that this would raise issues of multiple testing.  However, the advice was that if we used a Bonferroni correction in this case, most of the p values would be close to 1.  Instead, it was suggested looking at the size of the correlations to look at what was potentially interesting (i.e. strong positive or negative correlations-we therefore only discussed those with a r value >0.6 and p value <0.01).

### Radiation Exposure-medical physics report

This was prepared by Giles Morrison, Head of Radiology Physics at Sheffield Teaching Hospitals NHS Foundation Trust. The particpants were given written information about the radiation exposure in the patient information leaflets. (appendix 4)

The total x-ray dose arising from this study was approximately 106. 2 microSv. Therefore, participants receive an upper limit of approximately 106. 2 microSv, equivalent to approximately 18 days’ average natural background radiation (6.5 microSV per day is the natural background radiation). The Health Protection Agency Radiation Protection Divisiondescribe *a few week’s* natural background radiation as ‘Minimal Risk’, with between 1: 1,000,000 and 1: 100,000 lifetime additional risk of cancer. Using the whole population lifetime risk coefficient of 5. 7 x 10-2 Sv-1 (ICRP 103) this gives an additional risk of <1: 165,000. A dose constraint of 110 microSv should be applied to this group. However, it should be noted that patients recruited to this trial would be in the age range 13 – 16 years. For those < 16 years, because of their age the risks associated with the radiation exposures are greater than the same exposures in adults. The chances of children contracting a fatal cancer during their lifetime because of a radiation exposure in their childhood is considered to be up to a factor of x3 greater, falling to x1 by 16 years, compared to adults for the same exposure. However, the risk arising from the exposure in this study was unlikely to result in any identifiable health detriment. The potential radiation detriment resultant from this study was therefore deemed satisfactory. (included from the commissioned report)

### Ethics approval

I was registered the Principal Investigator (PS) for this study with Dr Neil Wright (Supervisor)as the Chief Investigator. Prior to successful ethics approval, the panel were provided with a research proposal, with requisite supporting documents. The documents submitted included a formal research proposal with covering letter, NHS research ethics application forms, a summary curriculum vitae of the chief investigator and principal investigator, parent information sheets for the parents, participant information sheets for 13-16 olds, and>16 year olds, a letter of invitation to the participants, G. P/Consultant information sheets and covering letter, a letter supporting the funding for the study, an advertisement about the study to appear in the local newspapers, questionnaires to be used in the study and a submission checklist.

The Sheffield Research Ethics Committee convened on the 19th of December 2011. Minor amendments to the protocol were requested (for example changing the lower limit to 13 years from 12 years), and ethical approval was granted in April 2012 once these changes were made (appendix 10).

To ensure that ethics and protocols were followed, the Principal investigator was trained in Good Clinical Practice as set out by the Inspections & Standards Division of the MHRA (EU Directive 2005/28/EC).

A minor amendment was submitted in 2013 requesting the following changes.

The exercise and science officer wanted to submit the project for a higher degree, and include focus group interviews at 12 months. We also wanted to include a payment for the young people attending their 12 and 18 month appointments to compensate for their time. This was granted approval (appendix 10).

Further progress reports were submitted in 2014 and 2015.

A declaration informing the end of the study will be submitted to the National Research Ethics Service at the end of December 2019 when all the papers are in and the PhD has been examined.

### Funding

The following bodies have granted funding for this study:

* CLAHRC South Yorkshire (£100,000) funded the project set up, balloon costs, hospital costs, travel expenses and sample analysis and the salary of the exercise and science officer.
* The bone work was primarily funded by the British Society of Pediatric Endocrinology and Diabetes National Research Award (£15000). There was a national call out for grant applications and a highly competitive process in which our application was one of two chosen out of nine that went through the second phase.

### Project steering meetings

Meetings were held on a regular basis (3-6 monthly) during the project with minutes and agenda recorded and circulated. These meetings were chaired and records kept by the PI (PS).

Regular meetings were also held with NPW, my educational supervisor on a fortnightly and monthly basis both to oversee the project and PhD progress.

The next 3 chapters will outline the results and discussion.

## Co-morbidity incidence, feasibility and engagement

### Recruitment Data

A total of 16 patients were interviewed.

* 2 declined to take part after initial discussion(16 year old female (white, T2DM) and q7 year old male (Arabic origin, pre diabetic)
* 1 was not suitable due to history of previous gastric surgery (Pyloric stenosis) revealed on detailed history taking (exclusion criteria) (14-year-old girl)
* 1 was not suitable due to not meeting the Tanner staging criteria and had Asperger’s. (inclusion criteria) (13-year-old boy)
* A total of 12 patients were recruited (5 males) over a period of 9 months (November 2012-July 2013).
* *Following the post viva feedback and discussion, I have emailed all the consultants in the surrounding hospitals who were contacted prior to the study. The two who referred patients to me have come back with some information. From memory, they think they discussed it with 1 (of a total of 8, 12.5 %) who did not wish to take part in the trial.*
* *We cannot be sure as some of the clinicians may have discussed it but not informed me when the patient did not show any interest.*

Process described in Figure 20.

Figure 20 - Flow chart looking at patient recruitment

* All patients had been obese for at least 5 years based on their history. Weight data 1 year prior to coming on the project showed an average weight gain of 11. 1 kg (range -4.5 to 21.3) in the year prior to balloon insertion and 20 kg gain in the 2 years prior to coming on the project.
* The mothers of 4 of the young people had bariatric surgery in the past.
* 9/12 young people had at least one parent who was obviously obese. One of the parents volunteered to be weighed at regular appointments to support their young person (BOB02 who was the participant with the most success in losing weight and keeping this off over the 2 years).
* Informed written consent and assent (if <16) were taken from all the parents and young people.
* All young people had taken part in a community weight management programme as a part of the inclusion criteria with limited success.
* All the young people had tried orlistat or sibutramine or both.

### Ethnicity, geography, family structure and socio-economic strata

* 10 of the 12-young people were White British.
* BOB10 was Black British.
* BOB04 was mixed race (White and black African).

All the young people lived in Yorkshire and Humber except 2 (BOB04 and BOB05) who were from Lincolnshire and Stockport respectively. However, only 3/12 young people lived locally in Sheffield.

#### Description of family structures and education

7/12 young people lived in a single parent household. One young person was adopted and looking to contact his birth family. 4 of the young people came alone for their appointments or with a friend/cousin from a few weeks after the balloon had been inserted. Five of the 12 young people had active CAMHs involvement. Two of the young people had history of self harm. Two of the young people were spending significant amounts of time caring for their mothers who were wheelchair bound. Only one young person was not in employment, education and training for over two years though one other young person had recently dropped out of college. Two of the young people were attending a specialist school provision for at least some of the week due to bullying and mental health issues. One young person developed alcohol dependence during follow up. Two of the young people were planning university. Two of the young people were working part time at the end of the study.

#### Socio-economic

* 11/12 families lived in areas of the highest deprivation (multiple deprivation quintiles 1 and 2) based on the Indices of multiple deprivation (2010).
* Only 2/12 of the families had parents doing white collar jobs.
* Discussion was had with all families about the intensity of the life style and exercise programme and the need to travel to Sheffield though some home visits were also planned. Travel expenses were reimbursed on production of receipts.

### Volunteer demographics and anthropometric data

* Mean body weight, mean BMI and BMI SDS at baseline with SD were 138. 45(SD=23. 9) Kg, 46. 43(SD=5. 6 kg/m2) and +4(SD=0. 3) ***(Table 7).***
* The lightest young person in the group weighed 107. 6 kg while the heaviest was 178. 8 kg.
* Mean age was 15. 3 years (range 13. 7-16. 5 years).
* Pre-op BMI ranged from 39. 6 to 56. 3. Mean BMI SDS was +4. 0 (where BMI SDS >3. 5 has been used to classify extreme obesity)(12).

Table 7 - Demographic data of BOB patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***No*** | ***Age/sex*** | ***Weight 1 yr prior*** | ***Pre-op weight (kg)*** | ***Pre-op BMI (kg/m2)*** | ***Pre-op BMI SDS*** |
| **BOB01** | 16.3/F | 122 | 130.9 | 46.8 | +4.1 |
| **BOB02** | 16.5/M | 157.6 | 178.8 | 52.8 | +4.3 |
| **BOB03** | 15.3/M | 130 | 145.9 | 49.3 | +4.1 |
| **BOB04** | 15.8/M | 128.6 | 147.2 | 42.1 | +3.7 |
| **BOB05** | 15.0/M | 133 | 154.9 | 51.6 | +4.2 |
| **BOB06** | 14.3/F | 106.6 | 107.6 | 46.8 | +4.1 |
| **BOB07** | 16.0/F | 121.4 | 116.9 | 41.8 | +3.7 |
| **BOB08** | 15.9/F | 141.6 | 161.8 | 49.1 | +4.2 |
| **BOB09** | 14.6/M | 112.6 | 118.9 | 44.1 | +3.9 |
| **BOB10** | 16/F | 104.4 | 115.7 | 39.6 | +3.6 |
| **BOB11** | 15.33/F | 146 | 170 | 56.3 | +4.5 |
| **BOB12** | 13.7/F | 120.2 | 117.7 | 39.5 | +3.6 |
| **MEAN** | 15.3 | 127 | 138.45 | 46.4 | +4.0 |
| **SD** | 0.9 | 16.1 | 23.9 | 5.6 | 0.3 |

**Tanner Staging:** All of them were classed as Tanner Stage 5 except BOB09 who was Tanner Stage 4 based on self-assessment.

**Bone age X-rays:** Some of the young people had bone age X-rays to confirm that they met eligibility criteria. All of them had a bone age over 15 years (boys) and 13 years (girls) and as expected for degree of obesity, had an advanced bone age. The table below depicts the Bone age compared to chronological age.

Table 8 - Bone Age vs Chronological Age Table

|  |  |  |
| --- | --- | --- |
| Patient | Chronological age (years) | Bone age (years) |
| BOB03 | 15. 57 | 16. 46 |
| BOB05 | 15. 06 | 16. 5 |
| BOB06 | 14. 38 | 14. 85 |
| BOB08 | 15. 86 | 16 |
| BOB09 | 14. 52 | 15. 22 |
| BOB10 | 16. 0 | 16. 23 |
| BOB11 | 15. 28 | 16. 0 |
| BOB12 | 13. 79 | 16. 0 |

Waist and hip circumference were also measured at all the follow up appointments.

Blood pressure was checked on the right arm three times using an appropriate sized cuff and the average of the 3 readings recorded.

Baseline waist and hip circumference along with blood pressure is depicted in Table 9

Table 9 - Waist, Hip circumference and Blood pressure at baseline

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No | Age/sex | Pre-op Waist (cm) | Pre op hip (cm) | Systolic (mm of hg) | Diastolic (mm of Hg) | Mean  (mm of hg) |
| BOB01 | 16. 3/F | 129. 5 | 157. 5 | 122 | 70 | 87 |
| BOB02 | 16. 5/M | 152. 4 | 160. 2 | 148 | 78 | 98 |
| BOB03 | 15. 3/M | 143. 5 | 134. 2 | 119 | 77 | 92 |
| BOB04 | 15. 8/M | 121. 9 | 130. 8 | 146 | 74 | 100 |
| BOB05 | 15. 0/M | 141. 2 | 127. 5 | 131 | 79 | 97 |
| BOB06 | 14. 3/F | 109. 2 | 125. 9 | 110 | 73 | 86 |
| BOB07 | 16. 0/F | 108. 7 | 133. 6 | 119 | 81 | 93 |
| BOB08 | 15. 9/F | 120. 5 | 148. 2 | 134 | 74 | 91 |
| BOB09 | 14. 6/M | 115. 8 | 131. 2 | 131 | 68 | 86 |
| BOB10 | 16. 0/F | 113. 5 | 116. 3 | 136 | 69 | 82 |
| BOB11 | 15. 3/F | 168. 3 | 143. 2 | 122 | 85 | 92 |
| BOB12 | 13. 7/F | 114. 5 | 126 | 115 | 69 | 84 |
| MEAN  SD | 15. 3  (0.9) | 128. 25  (19. 1) | 136. 22  (13. 38) | 127. 75  (11. 9) | 74. 75  (5. 36) | 90. 67  (5. 77) |

Mean waist circumference was 128.25 cm for girls and 136.2 cm for boys (above the >99.6th centile for both boys and girls).

Hip circumference for girls was 135.8cm giving a mean waist hip ratio of 0. 91 (WHO cut off is 0.85)

Mean waist/hip ratio (WHR) for boys was 135/136.8 equal to 0.99 (WHO cut off is 0.90)

All the boys had an increased WHR.

5/7 girls had increased WHR. If measurements are proportionately increased, the waist hip ratio could appear normal while still being excessive.

Waist hip ratios are shown separately in table 10 as normal values vary for males and females.

Table 10 - Waist hip ratio at baseline for boys and girls

|  |  |  |  |
| --- | --- | --- | --- |
| **Girls** | **Waist hip ratio** | **Boys** | **Waist hip ratio** |
| **BOB01** | 1. 1 | **BOB02** | 0. 91 |
| **BOB06** | 0. 84 | **BOB03** | 0. 96 |
| **BOB07** | 0. 8 | **BOB04** | 1. 0 |
| **BOB08** | 1. 2 | **BOB05** | 0. 93 |
| **BOB10** | 1. 15 | **BOB09** | 0. 95 |
| **BOB11** | 1. 1 |  |  |
| **BOB12** | 1. 04 |  |  |
| **Mean** | 0.91 |  | 0.99 |
| **SD** | 0.13 |  | 0.09 |

Young people provided a detailed medical history and a Source data form was used to document this and on-going visits (appendix 1). BOB02 and BOB04 had elevated blood pressure with systolic >140 mm of Hg.

### Co-morbidities

Co-morbidities were defined as detailed below.

* Hypertension was defined as systolic blood pressure greater than 95th centile for age, sex and height.
* Obstructive sleep apnoea (OSA) was documented as present if the young person reported symptoms of sleep disordered breathing or if a sleep study had been reported as abnormal. The young person in our study with OSA required non-invasive ventilation overnight. Sleep studies were not a part of the general work up.
* Genetic studies were also not a part of the assessment. None of the young people had early onset obesity necessitating this.
* Mobility issues were reported as described by the patient, as was school/college attendance.
* Insulin resistance was present based on HOMA-IR ≥4.4 or fasting hyperinsulinemia >120 or 180 depending on stage in puberty as per the OSCA guidelines.
* The participant was deemed to have psychosocial issues if there was previous/ongoing Child and Adolescent Mental Health services (CAMHS) involvement.
* Liver function and fasted lipid profiles formed part of the work up though a formal liver scan was not performed.
* Metabolic syndrome in adolescence is defined as a combination of risk factors which increase the likelihood of stroke and heart disease. In adolescence, 3 of the following would classify as risk factors(274)

1. Hypertension
2. Altered glucose metabolism
3. Dyslipidemia
4. Abdominal obesity-defined as waist circumference above the 90th centile for age and gender (275)

Based on the above definition, 5 of our young people had metabolic syndrome.

BOB02-Htn, raised HOMA, abdominal obesity, dyslipidemia

BOB03-Dyslipidemia, Abdominal obesity, Fasting HI

BOB04-Htn, abdominal obesity, peak insulin during ogtt was suggestive

Bob08-Raised HOMA, dyslipidemia and Abdominal obesity

BOB12-dyslipidemia, raised HOMA, Abdominal obesity

The young people had a range of weight related comorbidities.

* 5/12 (40%) of the young people had elevated liver enzymes (BOB02, BOB03, BOB04, BOB05 and BOB11) but only 2 were double the normal range.
* 6/12 had dyslipidemia (50 %), with elevated triglycerides 6/12), elevated cholesterol (1/12) or low HDL (4/12) (BOB02, BOB03, BOB05, BOB07, BOB08, BOB12). (see Table 10) Dyslipidemia was defined as in the OSCA guideline. (Cholesterol >5. 2, TGL>1. 47, HDL<1. 09)(12).
* 2/12 (16%) of the young people had high systolic readings though neither was on treatment for this (BOB02, BOB04) (see Table 9).
* 3/12 (25%) of the young people struggled to walk even short distances and described this as having a significant impact on their ability to exercise (BOB02, BOB09, BOB11).
* None of the young people had Type 2 diabetes but 75% had signs of insulin resistance based on their HOMA-IR values, the presence of acanthosis on examination or fasting hyperinsulinemia. (see Table 12)
* Only one young person was not in education, training or employment (NEET) (BOB02) though 4 of the others (BOB06, BOB08, BOB11, BOB12) were missing significant amounts of school because of bullying, behavioural and mental health issues.
* Almost half of the young people (5/12) had previous or ongoing CAMHS involvement though only one was on fluoxetine (BOB06) which was prescribed mid-way through the study
* One child was anaemic with documented iron deficiency anemia.

Vitamin D Status

* 5/12 young people had Vitamin D levels below 25 nmol/l classed as severe vitamin D deficiency. (see Table 11).
* 4/12 were between 25-50 classed as suboptimal.
* 1/12 between 50-75 classed as insufficiency
* Only 1/12 had normal levels of Vitamin D. (one unavailable)

Number of young people with co-morbidities is described in Figure 21

Table 11 - Hb, Liver function, Lipid profiles, Vitamin D status

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Hb | ALT | GGT | Cholesterol | Triglycerides | HDL | Vitamin D |
| BOB01 | 125 | 29 | 18 | 3. 8 | 0. 7 | 1. 1 | 23. 6 |
| BOB02 | 142 | **99** | 52 | 4. 7 | **1. 8** | **0. 9** | 9. 5 |
| BOB03 | 158 | **65** | 22 | **6. 1** | **2. 8** | **0. 8** | 19. 9 |
| BOB04 | 148 | **66** | 59 | 4. 5 | 1 | 1. 9 | 20. 4 |
| BOB05 | 157 | **63** | 47 | 4. 7 | **1. 5** | 1. 3 | 21. 7 |
| BOB06 |  | 30 | 23 | 3. 3 | 0. 7 | 1. 2 | 37. 2 |
| BOB07 |  | 48 | 46 | 4 | **1. 9** | 1. 6 | 65. 3 |
| BOB08 | 99 | 34 | 35 | 4 | **1. 6** | **0. 9** |  |
| BOB09 | 135 | 32 | 20 | 3. 7 | 1. 1 | 1. 2 | 28. 7 |
| BOB10 | 120 | 15 | 18 | 4. 7 | 1. 2 | 1. 1 | 33 |
| BOB11 | 140 | **71** | 36 | 4. 6 | 1 | **1.0** | 39. 4 |
| BOB12 | 148 | 16 | 28 | 4. 6 | **3** | 1. 1 | 116. 4 |
| Mean | 124. 6 | 47. 3 | 32. 9 | 4. 4 | 1. 5 | 1. 2 | 37. 3 |
| SD | 42. 9 | 25. 6 | 13. 1 | 0. 7 | 0. 75 | 0. 3 | 29. 9 |

Table 12 - Markers of insulin glucose metabolism pre-balloon (baseline)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | HOMA-IR | HBa1C  Mol/mol | Fasting Hyperinsulinemia  Pmol/l | Peak insulin level during OGTT  Pmol/l | Metabolic syndrome |
| BOB01 | 3. 04 | 34. 4 | 116 | 593 |  |
| BOB02 | **11. 9** | 39. 9 | **399** | **2805** | Yes |
| BOB03 | **4. 9** | 35. 5 | **170. 6** | **2153** | Yes |
| BOB04 | 1. 83 | 36. 6 | 65 | **2461** | Yes |
| BOB05 |  | 38. 8 |  |  |  |
| BOB06 | 2. 64 | 35. 5 | 96 | **925** |  |
| BOB07 | **4. 96** | 31. 1 | **194** | **840** |  |
| BOB08 | **14. 68** | 38. 8 | **534** | **3561** | Yes |
| BOB09 | 3. 76 | 35. 5 | 140 | **1164** |  |
| BOB10 | 4 | 37. 7 | **130** | **704** |  |
| BOB11 | **7. 6** | 37. 7 | **270** | **680** |  |
| BOB12 | **5. 13** | 33. 3 | **191** | **1251** | Yes |
| Mean | 5. 9 | 36. 2 | 209. 6 |  |  |
| SD | 4. 0 | 2. 5 | 141. 6 |  |  |

BOB05 was excluded from the OGTT analysis and incretin analysis as unfortunately they misunderstood the instructions and arrived after breakfast. He was still starved for 8 hours (ate at 7. 30 am) and tests done at 3: 30 pm in the afternoon instead of in the morning. They had travelled a 2-hour distance; therefore, it was not feasible to request them to come another day.

Raised HOMA-IR was seen in (5/12) BOB02, BOB07, BOB08, BOB11 and BOB12.

HBA1c was within normal range for all the young people (unaffected by fasting).

Fasting hyperinsulinemia was seen in 7/12 (BOB02, BOB03, BOB07, BOB08, BOB10, BOB11 and BOB12)

Peak levels >600 pmol/l were seen in 10/12 young people. Borderline high at 593 in BOB01. BOB05 excluded.

Figure 21 - Co-morbidities in BOB patients

### Feasibilty

**Tolerability:** The balloon was generally well tolerated. All patients (except one) experienced nausea, vomiting and abdominal discomfort in the first week. For 1 patient, these symptoms lasted 2 weeks. Another patient developed significant diarrhea 3 weeks later and attended A&E and had 2 extra visits for review. Tests for Clostridium Difficili were negative and ultrasound showed balloon was in place. One child developed a subconjunctival hemorrhage (following projectile vomiting) that resolved spontaneously.

**Complications:** No serious complications like balloon deflation, intestinal obstruction or perforation were seen. There were no early balloon removals.

**Adverse event:** One child took an overdose of paracetamol. This was brought to light to the PI only after several days by the mother in the context of a different conversation. The child had already been seen by her GP and CAMHS involvement was already in place. Appropriate paperwork and blood tests were completed. It was recorded as a case of deliberate self-harm unrelated to the project.

One young person (BOB12) was diagnosed with a psychotic illness 6 weeks after balloon removal and was withdrawn from the study after discussion within the team. Recorded as unrelated to the project.

### Patient engagement

Eight medical contacts were planned after balloon insertion and before removal and mean attendance was 6. 4 visits with only 2 patients attending fewer than 5 visits.

3 further medical visits took place at 12, 18 and 24 months from the start of the project.

10/12 young people attended for the final visit at 24 months (BOB12 was withdrawn from the study and BOB09 dropped out of the study)

38 visits (4+26+8 plus visits at 12, 18 and 24 months0 were planned within the lifestyle intervention before, during and after the balloon was removed with 3 follow up visits and an average of 14 visits took place.

Figure 22 shows the percentage of visits attended at SHU (lifestyle intervention) and SCH (children’s hospital for the medical visits). 2/3rd of patients had >80 percentage attendance for medical reviews.

In comparison, only 3/12 had over 50 percent attendance for the lifestyle programme.

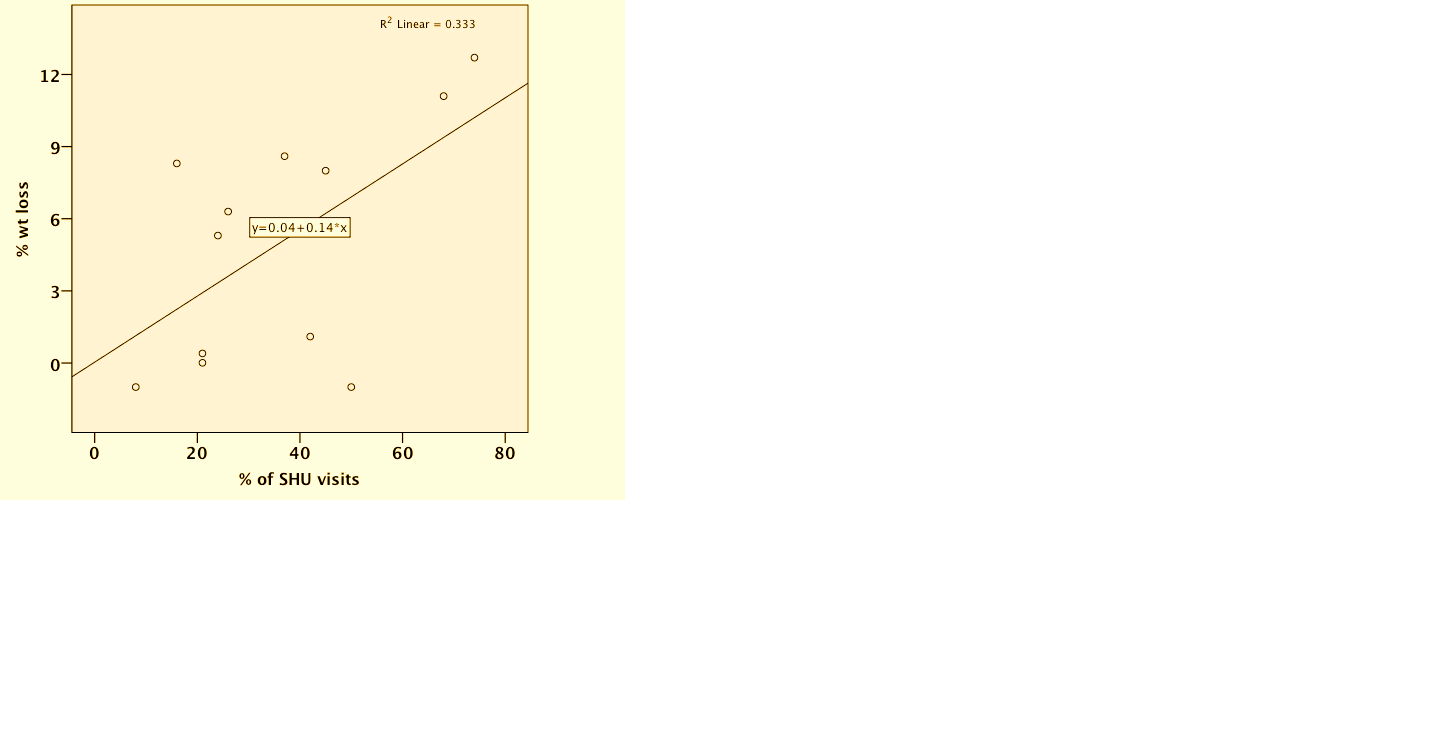
Figure 22 - Percentage of participant visits attended versus planned for lifestyle and medical review

Moderate correlation (r=0. 57) was seen between number of visits to see the exercise and science officer and weight change experienced as shown in Figure 22.

Issues with patient engagement persisted with 2 drop outs by 24 months (1 excluded, 1 drop out).

1 patient did not attend despite repeated appointments being offered (BOB09) and 1 young person needed admission for mental health issues and hence was excluded from the study (BOB12).

Figure 23 - Correlation between number of visits to the exercise and science officer and percentage of weight change experienced



### Discussion

#### Recruitment

Recruitment was slow and took about 8 months to complete (November 2012-July 2013). Significant liaison with paediatric teams/consultants from different hospitals was needed to identify young people who met the criteria for the study. However, advertisement within the hospital or in the local media was not required to meet targets though these leaflets had ethical approval. This was discussed at project meetings and with the hospital media team.

All balloon insertions were completed by August 2013 and removals by March 2014.

Challenges were ensuring that all individuals met the inclusion criteria and understood the commitment involved in the project. One child had to be turned away till they had attended a community-based intervention (BOB06). Another had previous gastric surgery, which is a contra-indication to the use of the balloon. One young person had not completed the majority of his growth and had a diagnosis of Asperger’s and therefore was not suitable for inclusion in the study. While he did not have learning difficulties, assent was a concern in his case and after multiple discussions with his neurodisability paediatrician regarding his coping mechanisms, it was decided to not include him in the project.

2 of the young people came and discussed the project but decided not to take part because of their worries about associated complications.

In a study looking at recruitment to adolescent obesity trials (Loozit), the authors found a 32 percent recruitment rate (276). Local newspapers and school newsletters were the most successful way to recruit and the main reasons to refuse were age (too young) or the adolescent refusing to participate even when parents expressed an interest. As our intervention was aimed at those at the extreme end of the spectrum, it was very likely that they would have had medical input, so while local adverts were prepared, these were not used. Seventy five percent of the YP who had the project discussed with them were recruited to the project (quite unusual for a major intervention study) which highlights the scarcity of options available to these young people(248).

#### Ethnicity, geography, family structure and socio-economic strata

Most of our young people were from white backgrounds with one black and one mixed race young person. This is as expected for the Yorkshire and Humber region from where most the young people came (277).

Though, ideally, we would have liked to recruit more locally, due to our presence at outreach clinics and discussions with colleagues, it seemed fair to accept referrals from outside the region so as not to preclude keen families though their motivation and willingness to travel were assessed repeatedly at the first few appointments.

Obesity is more common in the lower socioeconomic strata and severe obesity even more so(13), again our demographics are similarto what is reported in the literature.

Six out of the twelve young people were being brought up in single parent families (mothers). One couple were separated with regular contact with dad bringing the young person to appointments. Two of the mothers had significant disability and were in wheel chairs and would often wait downstairs when the young person came for their appointments due to the time taken to access the Clinical Research Facility. These 2-young people were providing a significant amount of care to their mothers’, though did not have formal recognition as young carers.

Several parents were also obese/overweight and had experience of bariatric surgery themselves increasing their acceptability of the intervention. However, this may have proved more of an issue as their expectations from the balloon were higher.

Children of obese parents are more likely to be obese(278). In the Early Bird 43 study looking at 226 trios born in 1995-96 in Plymouth, girls were 10 times more likely and boys six times more likely to be obese if the parent of the same sex was obese. This was also seen in our study with a significant number either overweight or obese (9/12). Only one parent volunteered to be weighed alongside her son at review appointments.

#### Volunteer Demographics and Anthropometry

It is clear from the description of the demographics that the young people recruited into the study were not the average overweight child, rather they were at the extreme end of the spectrum with a mean weight of 138 kg and a BMI SDS of +4.

There are very few studies tailored to looking at effective intervention in children with severe obesity as discussed previously and the common themes that emerged from meeting the families and young people were anger, frustration, upset, and feeling let down. Each of the young people had been obese for several years and had tried lifestyle interventions/medications with minimal benefit. The mean BMI/BMI SDS of our group is very like that described in the Treadwell systemic review of paediatric bariatric surgery and much higher than previously described balloon studies in adolescents (99)suggesting that bariatric surgery is a viable option for them(71).

Consistency in waist and hip measurements was maintained by trying to have no more than 1-2 trained health professionals doing it. The young people were so large that getting these done accurately was difficult. As expected in this degree of obesity, these measures were well above the 99. 6th centile on UK charts indicating high risk of diabetes, hypertension and cardiovascular risk independent of BMI. Some studies suggest that at BMI≥35, waist circumference has little added value, however we decided to monitor this and correlate changes if any with changes in blood pressure and insulin resistance. Two of the young people had normal ratios but this was because their measurements were so large, that the ratio normalized.

#### Comorbidity

Significant co-morbidities were noted in our group of young people. None of them had frank type 2 diabetes though 9/12 had elevated HOMA-IR indices and fasting HI. In a study of almost 2000 adolescents between 12-19 years, just above half were noted to have insulin resistance based on their HOMA-IR result ≥4.4. The young people in our study had a mean BMI of 4 SDS, which would explain the high degree of insulin resistance noted. Of course, HOMA-IR only measures insulin in the fasting state and therefore is not as sensitive as clamp studies which are however more difficult to perform(104).

Elevated liver enzymes can serve as a surrogate marker of non-alcoholic fatty liver disease (NAFLD) though this can occur without elevation of the aminotransferases. The prevalence of childhood NAFLD is estimated at 5-17 percent in the Western World and obesity, insulin resistance, impaired glucose tolerance may be present at diagnosis. (279)

In two and half thousand children between 12-18 years enrolled in the NHANES III survey, 6% of overweight, 10 percent of obese adolescents had elevated ALT levels with 1 percent having levels twice over normal. Other associations with elevated ALT levels included age, HBA1c, increased triglycerides, and decreased Vitamin E and C. (280)

5/12 (40 percent) of the young people in our cohort had elevated ALT and two had levels greater than 1.5 times normal. None of the children had elevated gamma GT.

Alcohol intake was occasional for all the young people except one who had significant issues. In the above study, 50 percent of obese adolescents who reported a modest alcohol intake (>4 times a month) had elevated ALT levels.

In a cross sectional study of 239 adolescents, (52% obese and 25% overweight), just over 1/3rd had elevated cholesterol and about 1/5th had hypertriglyceridemia and half had low HDL. Thus, our Dyslipidemia prevalence was lower for low HDL and hypercholesterolemia but higher for hypertriglyceridemia from those quoted in literature. (281) We have only a small cohort of 12, though level of obesity was extreme.

CAMHS involvement was as expected at 40 percent(25).

Several factors interact to significantly increase the risk of obstructive sleep apnoea (OSA) amongst obese children and adolescents which include increased prevalence of adenotonsillar hypertrophy, persistence of OSA after adenotonsillectomy, altered muscle tone and excess mechanical load on the chest wall(282). In a review of patients being assessed for bariatric surgery, (19/34), 55 % had OSA the severity of which markedly improved after weight loss(283). The young man in our study was advised nocturnal CPAP but compliance with this was poor.

A large cross sectional study showed the prevalence of high blood pressure in moderate obesity to be about 3. 8 percent rising to 9. 2 percent in extreme obesity with a backround prevalence of 0. 9 percent in normal weight adolescents(284). 2/12 YP had hypertension in our cohort but were not on treatment for this, though one of them was commenced on treatment during the study.

Though menstrual history was taken for all the girls and problems if any were documented with hirsutism and acne, we did not measure testosterone or do ultrasound scans to confirm polycystic ovarian disease.

The spectrum of co-morbidity seen in our cohort is as expected for the degree of obesity. We expected that given the degree of obesity, we may see 1-2 cases of type 2 diabetes (4 percent in obesity in Sinha paper) but this was not the case. We had one mixed race and one black young person in our cohort with the rest being white Caucasian where the risk is lower.

#### Feasibility

Intragastric balloons due to their temporary nature, and reversibility may have the potential to help to bridge the gap between ineffective community based interventions (in the context of severe obesity particularly), pharmaceutical options and permanent forms of bariatric surgery, for which there is limited long-term data. There are understandable concerns from pediatricians, commissioners and the public regarding the use of bariatric procedures in severely obese adolescents even though the postsurgical weight loss and safety profiles are not dissimilar to that reported in adults. This stems from the irreversible nature of the procedure in some cases, informed consent, concerns about malabsorption, compliance with supplementation and the long-term metabolic consequences including effect on skeletal health(285).

Previous adult systematic reviews and meta-analysis of intra-gastric balloons has shown that the cohort of patients experienced clinically significant weight loss. However, long term this was not sustained in at least half of the patients(96).

In our cohort, the balloon was well tolerated and safe with no early removals required in our cohort of young people. It required 3 days in hospital on average, hence minimized impact on school and other activities. We admitted the young person on a Friday morning and they were discharged either on the Saturday or Sunday. They could be back at school/college by Wednesday though several of them were not attending regularly in any case.

Vomiting and abdominal pain following the procedure were managed with regular anti spasmodic and anti-emetics. All but 3 young people (stayed in 2 days) were discharged the following day. Anecdotal experience from the adult bariatric surgeon suggested that the young people fared better in terms of side-effects when compared with their adult counter parts. Comparing this with other balloon studies(86), we found that our young people had a lower incidence of side effects and no early balloon removals were necessary.

#### Engagement

Adolescents are more likely to attend and engage if travel is minimal and the location convenient(286). For particularly 9/12 of our participants this was not the case. Parking issues at the hospital did not help though all travel expenses were reimbursed.

All agreed initially for the visits to ‘get the balloon’ but after that gradually the number of visits decreased. Having to get to 2 places (hospital appointment plus exercise lab) again were not popular and in retrospect, these should have been combined at one place depending on the focus of the appointment. Consistency of anthropometric measurements including the same machine for weight and height was one of the reasons for the 2 appointments.

Almost all attended the first few appointments with engagement declining as time went on. Factors identified to engage adherence include involvement of family (the family of the young person who was most successful during the project changed the way they cooked, the activities they did as a family and attended several sessions with him), fun and enjoyable interventions, online access to parts of the intervention and making it easier to attend(286).

Attendance at the medical appointments was far higher (80 percent versus 35 percent); perhaps these were perceived as more important. Those who attended more of the lifestyle intervention lost more weight (r=0. 57, p=0.05), and the focus of further studies should be on how best to improve this.

## Results Weight Loss, Comorbidity and Discussion

### Weight Loss

Twelve young people were recruited into the BOB Study (Balloons in Obesity study) over a period of 8 months. The intragastric balloon was supported by a weekly lifestyle support programme while the balloon was in situ. The balloon stayed in for a mean of 6 months. Average weight loss at 6 months was 7 kg (p=0. 005), with change in BMI of 2. 53 kg/m2 (p=0. 004) and BMI SDS reduction of 0. 2 (p=0. 002).

Average percentage weight loss at 6 months was 5%.

Excess percentage weight loss is often used to describe results in adult studies, however for ease of understanding and because some of our patients were still growing, percentage weight loss using total weight was used.

Table 13 show the Weight loss trajectory of all 12 patients expressed in terms of percentage of weight loss from starting weight.

Table 13 - Percentage weight change over 6 months (from baseline to 26 weeks)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| BOB Patients | Pre-op | 2 | 4 | 8 | 12 | 16 | 20 | 26 |
| BOB01 | 0 | -3. 2 | -7. 5 | -6. 9 | -7. 5 | -6. 2 | -8. 7 | -9.0 |
| BOB02 | 0 | -4. 8 | -6. 9 | -8. 2 | -9 | -9 | -10. 6 | -12. 7 |
| BOB03 | 0 | -4. 4 | -2. 9 | -3. 3 | -3. 3 | -2 | -1. 2 | -0. 4 |
| BOB04 | 0 | 0 | -2 | -3. 6 | -3. 3 | -1. 7 | -3. 4 | -5. 2 |
| BOB05 | 0 | -2. 8 | -2. 6 | -5. 2 | -6. 4 | -6 | -5. 8 | -8. 3 |
| BOB06 | 0 | -3. 6 | -6. 9 | -9 | -8. 5 | -9 | -9 | -11. 1 |
| BOB07 | 0 | -3. 3 | -5. 5 | -7 | -7 | -7. 5 | -6 | -8 |
| BOB08 | 0 | -3. 8 | -5 | -4. 4 | -4 | -2. 4 | -1. 3 | -1. 1 |
| BOB09 | 0 | -4. 6 | -3. 4 | -3. 4 | -3. 4 | -2 | 1 | 1 |
| BOB10 | 0 | -1 | -1 | -1. 5 | -2. 3 | 1. 02 | 1. 02 | 1. 02 |
| BOB11 | 0 | -0. 5 | -0. 5 | -1. 1 | 0 | -1. 5 | -0. 2 | -1. 1 |
| BOB12 | 0 | -2 | -3. 5 | -4. 1 | -6. 3 | -6. 8 | -6. 8 | -6. 3 |
|  |  |  |  |  |  |  |  | -5. 1 |

As is evident from other studies, most of the percentage weight loss took place in the first 3 months.

Figure 24 shows the weight loss percentage (calculated from total weight) in the first 6 months (n=12) with time since surgery on the x axis and percentage weight lost on the y axis.

Ten of the twelve young people lost weight in the 6 months the balloon was insitu (BOB09 and BOB10 were the 2 exceptions)

Figure 24 - Percentage weight change over 6 months

The range of weight loss was +2 to -23 kg.

Significant weight loss was seen in the first 2-4 weeks in all the young people (including 9 and 10 who did not lose weight over the 6 months) related to restrictions around diet when the balloon first went in, as well as due to the sickness that was experienced by 11/12 young people.

Further follow up:

At 12 months (6 months post balloon removal) mean weight was 138. 4 kg (±21. 7), same as mean weight when the project commenced.

However, weight loss was sustained or continued in only 2 participants at 24 months*.* Mean weight gain was 6kg (±22. 9) by 24 months (18 months after balloon removal).

Overall, mean percentage weight gain at 24 months was 5.5 (14.2) %.

Table 14 - Individual participant weights at 0, 6, 12, 18 and 24 months

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **BOB Patients** | **Baseline**  **(wt in kilos)** | **6/24 (wt at balloon removal)** | **12/24** | **18/24** | **24**  **(wt at 2 year follow up)** |
| **BOB01** | 130.9 | 119.8 | 128 | 127.5 | 137.3 |
| **BOB02** | 178.9 | 156.3 | 144.5 | 127.2 | 125.5 |
| **BOB03** | 145.9 | 145.4 | 153.7 | 153.4 | 161.5 |
| **BOB04** | 142.2 | 134.8 | 129.5 | 134.1 | 135.9 |
| **BOB05** | 154.9 | 142 |  |  | 163.9 |
| **BOB06** | 107.6 | 95.7 | 109 | 120.2 | 127.1 |
| **BOB07** | 116.9 | 107.6 | 115.1 | 114.8 | 120.6 |
| **BOB08** | 161.8 | 160.1 | 175.6 | 177.5 | 182.3 |
| **BOB09** | 118.9 | 119.4 | 129.6 | 137.1 |  |
| **BOB10** | 115.7 | 117.7 |  | 181.1 | 137.1 |
| **BOB11** | 170 | 168.2 | 160.6 |  | 193 |
| **BOB12** | 117.7 | 110.3 |  |  |  |
| **Mean(sd)** | 138.5(23.9) | 131.4  (23.1) | 138.4(21.9) | 140.5(22.9 | 148.4(25.2) |
| **Mean (sd)**  **(9/12 ex)** | 142.5  (24.3) | 134.8  (23.9) |  |  | 148.4 (25.2) |
| **P values**  **(1/2)** | P 0.005\*  P=0.009\* |  |  |  |  |

Figure 25 shows the percentage weight loss (gain) over the course of the 2 years (data points 12,26, 52,78 and 104 weeks) (n=10).

Figure 25 - Percentage weight change at 104 weeks (24 months, 18 months post balloon removal)

Only participant BOB02 and BOB04 had a weight below baseline at 24 months.

Some of the participants started putting the weight back on within a few weeks of the balloon coming out. Several were still below baseline at 1 year (BOB01, BOB07,BOB11).The lifestyle support was offered weekly for 4 weeks prior to balloon insertion, the 26 weeks while the balloon was in situ and 8 weeks thereafter though as previously discussed, engagement with this was mixed.

All the young people had shown a steady weight gain prior to coming on the project and weight in the 2 years’ pre-study and post study is contrasted in Figure 16.

The young people had gained a mean of 11 (9.5) kg in the year prior to the study and a review of their earlier growth charts were similar. Only BOB12 and BOB07 had limited success with losing weight with a lifestyle intervention in the year prior to the study, however had then plateaued and started putting on weight again. Figure 25 shows the weight trajectory the 2 years before coming on the programme and the 2 years on the study.

Figure 26 - Individual Percentage weight change in the 2 years prior to the balloon insertion followed by two years during the project

The young people had gained a mean of 20 kg (mean 14 percent) in the 2 years before coming on the project. The intra-gastric balloon placement and the intensive life style intervention stemed this trend for the 6 months the balloon was in situ, however, this trend continued for 8/10 participants at 2 years.

Mean weight gain 2 years prior to the project, the loss in the 6 months the balloon was in situ with further increase is shown in Figure 27. (n=12 at all time p0ints except 104 weeks when it was n=10)

Figure 27 - Mean percentage weight change 2 years before and after the procedure

### Waist and hip change over the 2 years

Waist and hip circumference measurement was planned for each patient at 5 time points (baseline, 6 months at balloon removal, 12 months, 18 months and 24 months).

Table 15 - Changes in waist circumference over the 24 months for individual participants

(Means, SD and p value when comparing baseline and 6 months, and baseline and 24 months).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **BOB Patients** | **Baseline** | **6 months** | **12 months** | **18 months** | **24 months** |
| **BOB01** | 129.5 | 110.5 | 113 | 115 | 137 |
| **BOB02** | 152. 4 | 117. 2 | 107 | 102. 5 | 115 |
| **BOB03** | 143. 5 | 138. 6 | 139 | 143 | 146. 9 |
| **BOb04** | 121. 9 | 115. 4 | 114. 5 | 118. 5 | 121. 5 |
| **BOB 05** | 141. 2 |  |  |  | 141. 6 |
| **BOB06** | 109. 2 | 92. 4 | 110. 5 | 118 | 122. 5 |
| **BOB07** | 108. 7 | 95. 5 | 107. 5 | 114 | 112 |
| **BOB08** | 120. 5 | 123 | 134 | 145 | 167. 5 |
| **BOB09** | 115. 8 | 111 | 110 | 113. 1 |  |
| **BOB10** | 113. 5 | 123. 3 |  | 145. 6 | 150. 2 |
| **BOB11** | 168. 3 | 141. 5 | 140 | 145. 3 | 173 |
| **BOB12** | 114.5 | 106 |  |  |  |
| **Mean** | 128.25 | 112.6 | 119.5 | 126 | 134.3 |
| **SD** | 19.1 | 7.3 | 13.9 | 16.7 | 28.1 |
| **P value 0-6 months** | 0.02\* |  |  |  |  |
| **P value 0-24 months** | 0.3 |  |  |  |  |

There was a significant drop in the waist circumference at 6 months (p=0. 02), it went back to baseline 1 year post balloon removal and exceeded baseline at 18 months’ post balloon removal.

Hip circumference fell by a mean 3. 05 cm following intra-gastric balloon therapy as is seen below but this was not significant. It exceeded baseline at 24 month follow up.

Table 16 - Changes in hip circumference over the 24 months for individual participants

(Means, SD and p value when comparing baseline and 6 months, and baseline and 24 months).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patients** | **Baseline** | **6 months** | **12 months** | **18 months** | **24 months** |
| **BOB01**  **BOB02**  **BOB03**  **BOB04**  **BOB05**  **BOB06**  **BOB07**  **BOB08**  **BOB09**  **BOB10**  **BOB11**  **BOB12**  **Mean**  **SDS**  **Mean (girls**  **SD (girls)**  **Mean (boys**  **SD (boys)**  **P value(0-6)**  **Pvalue (0-24\_** | 157. 5  160. 2  134. 2  130. 8  127. 5  125. 9  133. 6  148. 2  131. 2  116. 3  143. 2  126  136. 22  13. 38  135. 8  14. 4  139. 1  13. 3  0. 3  0. 9 | |  | | --- | | 137 | | 144 | | 135 | | 118. 2 | | missing | | 119. 8 | | 126. 4 | | 142 | | 133 | | 129. 3 | | 118  133.2 | | 13.2  132.1 | | 16.2 | | | 132.6  10.7 | | |  | | |  | | | |  | | --- | | 137 | | 140 | | 139. 5 | | 118. 5 | | missing | | 134. 6 | | 132. 4 | | 158. 3 | | 136 | |  | | 158 | |  | | 139. 37  12. 4 | | |  | | | |  | | --- | | 144 | | 130 | | 143. 5 | | 121. 5 | | missing | | 145 | | 135 | | 159 | | 129. 5 | | 126. 9 | | 169 | |  | | 140. 34 | | | 14. 9 | | | |  | | --- | | 122 | | 126. 5 | | 152. 8 | | 121 | | 153 | | 146 | | 140. 6 | | 140. 8 | |  | | 130. 8 | | 151. 5 | |  | | 138. 5 | | | 2. 6 | | |

### Blood pressure

Systolic, diastolic and mean blood pressures were all lower at 6 months when the balloon was removed. Systolic blood pressure fell by 5. 8mmHg (SD16. 8, p=0. 27). Diastolic blood pressure fell by 2. 0 mmHg (SD 10. 9, p=0. 57). Of the two patients with established hypertension, in one subject blood pressure normalized at 6 months. The second patient was started on medication at his local hospital.

As patients regained weight after balloon removal, systolic and mean blood pressures subsequently rose and were above baseline levels at 24 months. However, improvements in diastolic blood pressure were maintained.

There was a moderate positive correlation between absolute weight loss and change in systolic pressure (r= 0. 3) and diastolic pressure (r=0. 4) at 6 months. There was also a positive correlation between change in waist circumference and drop in diastolic blood pressure at 6 months (r=0.56)

4 of the young people were being investigated at their local units for high blood pressure at the 2 year follow up (18 months after balloon removal).

Table 17 - Individual BP measurements at baseline, 6 months (balloon removal) and 24 months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Bob patients | Baseline  Systolic | Baseline  Diastolic | Baseline  Mean | 6 m  Systolic | 6 m  Diastolic | 6m  Mean | 24 m  Systolic | 24 m  Diastolic | 24m  Mean |
| BOB01 | 122 | 70 | 87 | 107 | 78 | 88 | 119 | 64 | 86 |
| BOB02 | **148** | 78 | 98 | 112 | 68 | 83 | 124 | 65 | 82 |
| BOB03 | 119 | 77 | 92 | 137 | 96 | 104 | **145** | 76 | 102 |
| BOB04 | **146** | 74 | 100 | 147 | 83 | 102 | **153** | 74 | 102 |
| BOB05 | 131 | 79 | 97 | 130 | 64 | 88 | **152** | 77 | 104 |
| BOB06 | 110 | 73 | 86 | 122 | 67 | 84 | 119 | 81 | 94 |
| BOB07 | 119 | 81 | 93 | 110 | 65 | 80 | 94 | 62 | 76 |
| BOB08 | 134 | 74 | 91 | 140 | 78 | 96 | 136 | 84 | 100 |
| BOB09 | 131 | 68 | 86 | 103 | 68 | 82 | N/A | N/A | N/A |
| BOB10 | 136 | 69 | 82 | 125 | 74 | 91 | 137 | 68 | 93 |
| BOB11 | 122 | 85 | 92 | 135 | 69 | 90 | **143** | 69 | 97 |
| BOB12 | 115 | 69 | 94 | 98 | 64 | 78 | N/A | N/A | N/A |
| Mean  (sd) | 127. 8  (11. 9) | 74. 8  (5. 4) | 90. 7  (5. 8) | 122. 2  (16) | 72. 8  (9. 6) | 88. 8  (8. 3) | 132. 2  (18. 3) | 72  (7. 5) | 94. 2  (8. 8) |
| P value  0-6 mth  0-24 mth | 0. 27  0. 54 | 0. 57  0. 22 | 0. 46  0. 44 |  |  |  |  |  |  |

### Glucose and Insulin metabolism

Several parameters were used to assess glucose and insulin metabolism including fasting insulin, peak insulin during the OGTT and HOMA-IR. None of the young people had impaired glucose tolerance or type 2 diabetes.

None of the young people had a raised fasted blood glucose. **Mean Glucose at 60 minutes was significantly lower at 6 months at balloon removal. (p=0.01)**

There were no changes in the glucose levels at 0 and 24 months.

There was no change in the Glucose (area under the curve) at the 3 time points.

Mean glucose levels at baseline, balloon removal and 24 months are shown in Figure 28.

Figure 28 - Mean Glucose at baseline, 6 months at balloon removal and at 24 month follow up with error bars

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **Baseline** | | | | | **6 months** | | | | | **24 months** | | | | |
|  | **0** | **30** | **60** | **90** | **120** | **0** | **30** | **60** | **90** | **120** | **0** | **30** | **60** | **90** | **120** |
| **BOB01** | 116 |  | 314 | 314 | 593 | 80 | 218 | 604 | 543 | 343 | 87 | 116 | 473 | 671 | 411 |
| **BOB02** | 399 | 717 | 835 | 2805 | 75 | 373 | 2016 | 1044 | 264 | 1126 | 105 | 658 |  | 200 | 570 |
| **BOB03** | 171 | 1380 | 2153 | 1872 | 349 | 239 | 461 | 72 | 90 | 224 | 168 |  | 681 | 1181 | 1134 |
| **BOB04** | 65 | 567 | 1204 | 2461 | 708 | 253 | 1863 | 1118 | 1225 | 857 | 165 | 275 | 677 |  | 849 |
| **BOB05** |  |  |  |  |  |  |  |  |  |  | 287 |  |  | 1309 | 1091 |
| **BOB06** | 96 | 925 |  | 327 | 282 | 152 | 85 | 32 | 44 | 104 | 321 | 552 | 735 | 395 | 378 |
| **BOB07** | 194 | 221 | 840 | 169 | 436 | 102 | 491 | 471 | 286 | 383 | 151 | 494 | 801 |  | 575 |
| **BOB08** | 534 | 2915 | 3561 |  | 411 | 379 | 2403 |  |  | 435 | 432 | 2713 | 2551 | 3247 | 2254 |
| **BOB09** | 140 | 1164 | 1012 | 517 | 953 | 18 | 60 | 65 | 78 | 43 |  |  |  |  |  |
| **BOB10** | 130 | 704 | 401 | 505 | 514 | 184 | 524 | 1101 | 633 | 363 | 187 | 1094 | 940 | 575 | 210 |
| **BOB11** | 270 | 83 |  | 107 | 680 | 203 | 217 | 529 | 301 | 669 | 233 | 932 | 1178 | 1105 |  |
| **BOB12** | 191 | 39 | 1251 | 1198 | 236 | 95 | 188 | 268 | 302 | 387 |  |  |  |  |  |
| **Mean** | 210 | 872 | 1286 | 1028 | 476 | 189 | 775 | 530 | 377 | 449 | 214 | 854 | 1005 | 1085 | 830 |
| **SD** | 142 | 844 | 1009 | 1004 | 248 | 116 | 870 | 433 | 354 | 322 | 106 | 816 | 658 | 958 | 621 |
| **p value 0-6** | 0.52 | 0.88 | 0.24 | 0.05 | 0.85 |  |  |  |  |  |  |  |  |  |  |
| **p value 0-24** | 0.78 | 0.63 | 0.26 | **0.**58 | 0.16 |  |  |  |  |  |  |  |  |  |  |

Table - Insulin levels during the OGTT at the 3 time points.

Changes in Insulin during the OGTT at 0,30,60,90 and 120 minutes are seen in Table 17.

Mean Insulin at 90 minutes was significantly lower at 6 month at balloon removal compared to baseline (p<0. 05).

There was no change in any other insulins and the significant change seen between 0-6 months at 90 minutes was not sustained at 24 months.

Mean insulin at baseline, 6 months at balloon removal and at 24 months are shown in Figure 28.

Figure 29 - Mean Insulin at baseline, 6 months at balloon removal and at 24 month follow up with error bars

There was a significant change in the mean insulin AUC between 0-6 months (p<0.05). (3122(sd 2076) versus 2173(sd 1845)). Mean insulin AUC for individual patients at baseline, 6 months and 24 months is shown in Figure 29.

Figure 30 - Mean AUC Insulin at baseline, 6 months at balloon removal and at 24 month follow up with error bars for individual participants

Table 19 - Change in Fasting hyperinsulinemia and peak insulin during OGTT at 0, 6 and 24 months (pmol/l)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | 0 months | 6 months | 24 months | 0 months | 6 months | 24 months |
| BOB01 | 116 | 80 | 87 | 593 | **604** | **671** |
| BOB02 | **399** | **373** | 105 | **2805** | **2016** | **658** |
| BOB03 | **170. 6** | **239** | **168** | **2153** | 461 | **1181** |
| BOB04 | 65 | **253** | **165** | **2461** | **1863** | **849** |
| BOB05 |  |  |  |  |  |  |
| BOB06 | 96 | **152** | **321** | **925** | 152 | **735** |
| BOB07 | **194** | 102 | **151** | **840** | 491 | **801** |
| BOB08 | **534** | **379** | **432** | **3561** | **2403** | **3247** |
| BOB09 | 140 | 18 |  | **1164** | 78 |  |
| BOB10 | **130** | **184** | **187** | **704** | **1101** | **1094** |
| BOB11 | **270** | **203** | **233** | **680** | **669** | **1178** |
| BOB12 | **191** | 95 |  | **1251** | 387 |  |
| Mean (sd) | 209. 6(141) | 188. 9(116. 5) | 213. 6(106. 4) | 1557. 9  1016. 5 | 929. 5  803. 9 | 1157. 1  810. 7 |
| P value | 0. 5 |  |  | 0. 006\* |  |  |

Though the mean fasting insulin at 6 months was lower than at baseline, this drop was not significant.

7/11 had fasting hyperinsulinemia at baseline. It improved for 2 of them at 6 months’ post balloon removal. 7/9 had fasting HI at 24 months.

**There was a significant difference between the peak insulin reached between visit 1 and visit 2 (baseline and post balloon insertion when mean 5% weight loss was experienced. (p=0. 006)**

**Insulin resistance as defined by HOMA-IR**

HOMA –IR ≥4. 4 as per OSCA was used as a marker for insulin resistance.

After 6 months of balloon therapy, BOB02, BOB03, BOB04, BOB06, BOB08 and BOB11 had elevated HOMA but BOB07 and BOB12 who had it at baseline did not.

At 24 months, of 9, only 1 and 2 did not have elevated HOMA-IR.

**Peak insulin**

**High OGTT peak defined as >600 as per OSCA guidance(12) at any time during the test was seen in all the YP except BOB01.**

BOB03, BOB06, BOB07, BOB09 and BOB12 had peaks < 600 pmol/l at 6 months.

At 24 months, all 9 (BOB05, BOB09, BOB12 excluded) had peaks greater than 600.

BOB05 data for 1st OGTT was excluded as he arrived after eating breakfast. Bloods were done 8 hours after at 3 pm in the afternoon as it was not possible for them to attend on a different day (lived over 2 hours away).

Table 20 - Change in HOMA-IR and HBA1C at 0, 6 and 24 months

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HOMA-IR** | | | **HBA1C** | | |
| **Patients** | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 3.04 | 2.1 | 2.9 | 34.4 | 34.4 | 31.1 |
| **BOB02** | **11.9** | **10.7** | 3.6 | 39.9 | 35.5 | 33.3 |
| **BOB03** | **4.9** | **6.57** | **5.2** | 35.5 | 34.4 | 34.4 |
| **BOB04** | 1.83 | **7.6** | **6** | 36.6 | 35.5 | 33.3 |
| **BOB05** |  |  | **10.2** | 38.8 | 35.5 | 36.6 |
| **BOB06** | 2.64 | 4.37 | **13.3** | 35.5 | 32.2 | 35.5 |
| **BOB07** | **4.96** | 2.68 | **4.9** | 31.1 | 34.4 | 31.1 |
| **BOB08** | **14.68** | **9.2** | **13.4** | 38.8 | 38.8 | 34 |
| **BOB09** | 3.76 | 0.52 |  | 35.5 | 35.5 |  |
| **BOB10** | 4 | **5.1** | **6.9** | 37.7 | 36.6 | 35 |
| **BOB11** | **7.6** | **5.84** | **7.9** | 37.7 | 36.6 | 37 |
| **BOB12** | **5.13** | 2.37 |  | 33.3 | 32.2 |  |
| **Mean** | **5.9** | **5.2** | 7.4 | 36.2 | 35.1 | 34.1 |
| **SD** | 4.0 | 3.2 | 3.8 | 2.5 | 1.8 | 2 |
| **p value 0-6** | 0.5 |  |  | 0.08 |  |  |
| **P Value**  **0-24** | 0.6 |  |  | 0.005\* |  |  |

Of the 7 individuals with raised HOMA-IR at balloon insertion 2/7 showed sufficient improvement that their markers of insulin resistance normalized.

As individuals tended to regain weight following balloon removal HOMA-IR scores and fasting insulin levels increased but Insulin AUC remained below pre-intervention levels.

There was also a fall in HBA1c at 6 months that was maintained despite weight regain (p=0.005). See Table 24

There was an association between the initial weight loss and improvements in insulin glucose metabolism (AUC insulin r=0. 3, HBA1c r=0. 4). This association was stronger at 24 months (AUC insulin r=0. 66 and HBA1c r=0. 64).

### Lipid profile

Table 21 - Change in Lipid profile at 0, 6 and 24 months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **TGL** | | | **Cholesterol** | | | **HDL** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 0. 7 | 0. 9 | 0. 8 | 3. 8 | 3. 5 | 3. 7 | 1. 1 | **1** | 1. 1 |
| **BOB02** | **1. 8** | **3. 3** | 1. 1 | 4. 7 | 4. 7 | 3 | **0. 9** | **0. 9** | **0. 8** |
| **BOB03** | **2. 8** | **2. 9** | **2. 9** | **6. 1** | **5. 2** | **5. 7** | **0. 8** | **0. 7** | **0. 9** |
| **BOB04** | 1 | 1. 2 | 0. 8 | 4. 5 | 3. 8 | 3. 9 | 1. 9 | 1. 5 |  |
| **BOB05** | **1. 5** | **2. 1** | **1. 6** | 4. 7 | 3. 5 | 4. 5 | 1. 3 | 1. 1 | 1. 2 |
| **BOB06** | 0. 7 | 0. 8 | 0. 7 | 3. 3 | 3. 6 | 3. 8 | 1. 2 | 1. 2 | 1. 3 |
| **BOB07** | **1. 9** | **1. 8** | **1. 6** | 4 | 3. 7 | 3. 7 | 1. 6 | **0. 8** | 1. 1 |
| **BOB08** | **1. 6** | **1. 7** | **1. 5** | 4 | 4. 9 | 4. 6 | **0. 9** |  | **0. 8** |
| **BOB09** | 1. 1 | **2. 5** |  | 3. 7 | 3. 7 |  | 1. 2 | 1. 4 |  |
| **BOB10** | 1. 2 | 1. 1 | 1. 1 | 4. 7 | 5 | 4. 8 | 1. 1 | 1. 2 | 1. 2 |
| **BOB11** | 1 | **2. 4** | 1. 3 | 4. 6 | 4. 2 | 5 | **1** | **0. 9** | 1. 1 |
| **BOB12** | **3** | **2** |  | 4. 6 | 3. 7 |  | 1. 1 | **0. 8** |  |
| **Mean** | 1. 525 | 1.89 | 1. 34 | 4.39 | 4. 125 | 4. 27 | 1. 175 | 1.05 | 1.06 |
| **SD** | 0.75 | 0.80 | 0.64 | 0.72 | 0.64 | 0.79 | 0.31 | 0.26 | 0.18 |

There was a fall in cholesterol of 0. 3 (CI-0. 85,0. 25) with a medium effect size that was not sustained at two years. There was a rise in triglycerides at 6 months, which was not sustained at 2 years; the reasons for this are unclear. Dyslipidemia did not resolve in the 6 individuals with baseline anomalies.

### Liver Enzymes

Most individuals had normal liver function at balloon insertion. 5/12 had ALT above the range. Of the two individuals with deranged ALT (as defined as 1.5 times upper end of normal), one normalized (BOB02). A further young person developed raised ALT at the end of the study (BOB03).

Mean Gamma glutamyl transferase levels fell significantly at 6 months (p=0.03) and remained below baseline levels at 24 months.

Table 22 - Liver profile at baseline, 6 months’ balloon removal and 24 month follow up

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **ALT** | | | **GammaGT** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 29 | 19 | 25 | 18 | 16 | 16 |
| **BOB02** | **99** | 66 | 43 | 52 | 32 | 18 |
| **BOB03** | **65** | 81 | **103** | 22 | 30 | 37 |
| **BOB04** | **66** | 43 | 40 | 50 | 38 | 24 |
| **BOB05** | **63** | 74 | 48 | 47 | 42 | 53 |
| **BOB06** | 30 | 34 | 14 | 23 | 13 | 24 |
| **BOB07** | 48 | 28 | 57 | 46 | 17 | 22 |
| **BOB08** | 34 | 44 | 37 | 35 | 32 | 42 |
| **BOB09** | 32 | 9 |  | 20 | 22 |  |
| **BOB10** | 15 | 27 | 28 | 18 | 20 | 19 |
| **BOB11** | **71** | 68 | **93** | 36 | 31 | 39 |
| **BOB12** | 16 | 23 |  | 28 | 17 |  |
| **Mean** | 47.3 | 43 | 48. 8 | 32.9 | 25.8 | 29. 4 |
| **SD** | 25.6 | 23. | 28. 7 | 13.1 | 9.5 | 12.5 |
| **P value 0-6** | 0.4 |  |  | 0.03\* |  |  |
| **P value**  **0-24** | 0.7 |  |  | 0.3 |  |  |

There were no significant changes between mean ALT at the 3 time points though the mean dropped by 4.3 at 6 months.

### Vitamin D

Vitamin D deficiency (Vitamin D <25 nmol/l) was present in 5 young people at baseline (BOB01-05) and suboptimal (between 25-50) in 4 others (BOB06, BOB09, BOB10, BOB11).

but only one subject at 24 months had Vitamin D <25 nmol/l. All the young people were asked to take a multivitamin capsule containing 1000 IU of Vitamin D for the 6 months the balloon was in situ. Subsequent prescriptions were done by the GP. Adherence was variable with only half taking the capsule for the full 6 months. However, there was no objective way of confirming this.

Table 23 - Vitamin D levels at baseline, 6 months and 24 months

|  |  |  |  |
| --- | --- | --- | --- |
| **Patients** | **Vitamin D** | | |
|  | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 23.6 | 52.9 | 28.4 |
| **BOB02** | 9.5 | 35.1 | 35.1 |
| **BOB03** | 19.9 | 49.4 | 39.2 |
| **BOB04** | 20.4 | 31.9 | 30.1 |
| **BOB05** | 21.7 | 63.3 | 69.3 |
| **BOB06** | 37.2 | 46.6 | 43 |
| **BOB07** | 65.3 | 37.8 | 52.9 |
| **BOB08** |  | 21.5 | 28.3 |
| **BOB09** | 28.7 | 11.6 |  |
| **BOB10** | 33 | 13.8 | 41 |
| **BOB11** | 39.4 | 18.5 | 16 |
| **BOB12** | 116.4 |  |  |
| **Mean** | 37.7 | 34.7 | 38.3 |
| **SD** | 29.9 | 17.1 | 14.8 |

### Thyroid Function

One child had autoimmune hypothyroidism. Compliance with treatment was poor. Her data has been excluded from analysis.

Table below shows change in TSH and T4 at baseline, at balloon removal at 6 months and at 24 months.

Table 24 - Thyroid Function Test at 0, 6 and 24 months

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **TSH** | | | **T4** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 2.9 | 2.12 | 3.6 | 10.9 | 16.1 | 11.2 |
| **BOB02** | 0.71 | 1.04 | 0.61 | 15.9 | 15.3 | 14.6 |
| **BOB03** | 6.6 | 3.35 | 3.6 | 12.1 | 13.4 | 13.8 |
| **BOB04** | 1.03 | 0.83 | 1.04 | 12.5 | 12.6 | 12.9 |
| **BOB05** | 1.58 | 0.68 |  | 11.7 | 16.5 | 12.3 |
| **BOB06** | 1.39 | 1.13 | 2.47 | 12.1 | 12.4 | 11.9 |
| **BOB07** | 2.99 | 1.83 | 2.12 | 14.2 | 12.9 | 12.7 |
| **BOB08** |  |  |  |  |  |  |
| **BOB09** | 1.37 | 1.64 |  | 10 | 11.2 |  |
| **BOB10** | 0.88 | 1.07 | 0.71 | 11.1 | 13.3 | 10.7 |
| **BOB11** | 0.16 | 2.64 | 4.86 | 12.8 | 13.6 | 11.2 |
| **BOB12** | 0.27 | 2.05 |  | 12.8 | 18.6(h) |  |
| **Mean** | 1.81 | 1.67 | 2.38 | 12.37 | 13.73 | 12.37 |
| **SD** | 1.84 | 0.83 | 1.55 | 1.62 | 1.71 | 1.28 |

There was no significant change in the other parameters (Vitamin A, Vitamin E, calcium).

The mean changes in weight, BMI, BMI SDS, waist and hip circumference, blood pressure, lipid profiles, HBA1c with SDS are listed in the table below. **Weight, BMI, BMI SDS, waist circumference and insulin AUC (area under the curve)** all changed significantly following the intervention.

### Summary

Table 25 - Change in mean anthropometric indices and metabolic parameters at baseline,6 and 24 months (24)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Before Balloon insertion**  **N=12**  **Mean (±SDs)** | **At 6 months after Balloon removal**  **N=12**  **Mean ((±SDs)** | **At 2 years-18 months post balloon removal**  **N=10**  **Mean ((±SDs)** | **Mean difference between baseline and balloon removal at 6 months**  **(95 CI)**  **[p value]** | **Mean difference between baseline and**  **24months**  **(95 CI)**  **[p value]** |
| **Body**  **weight (kg)** | 138.5  (23.9) | 131.4  (23.1) | 148.4  (25.2) | -7.1  (-27,12.8)  [p=0.005] \* | +9.9  (-11.8,31.8)  [p=0.4] |
| **BMI**  **(kg/m2)** | 46.4  (5.6) | 43.9  (5.5) | 49.3  (8.1) | -2.5  (-7.2,2.2)  [p=0.004] \* | +2.9  (-3,8.8)  [p=0.5] |
| **BMI SDS** | 4  (0.3) | 3.8  (0.3) | 4.2  (0.5) | -0.2  (-0.37, -0.03)  [p=0.002] \* | +0.2  (-0.1,0.5)  [p=0.5] |
| **Waist circumference**  **(cm)** | 128.3  (19.1) | 115.9  (15.6) | 138.7  (21.2) | -12.4  (-27.2, 2.4)  [p=0.016] \* | +10.4  (-6.7,27.5)  [p=0.3] |
| Systolic BP (mm of Hg) | 127.8  (11.9) | 122  (16) | 132.2  (18.3) | -5.8  (-17.7,6.1)  [p=0.3] | +4.4  (-9.1, 17.1)  [p=0.5] |
| Diastolic BP (mm of Hg) | 74.8  (5.4) | 72.8  (9.5) | 72(7.5) | -2.0  (-8.5,4.5)  [p=0.6] | -2.8  (-8.3, 2.3)  [p=0.2] |
| Fasting glucose (mmol) | 4.3  (0.3) | 4.3  (0.3) | 4.7  (0.4) | -0.03  (-0.25,0.25)  [p=0.5] | +0.4  (0.1,0.7)  [p=0.1] |
| Fasting  Hyperinsulinemia(pmol/l) | 209.6  (141.6) | 189  (116.4) | 213.6  (106.4) | -20.6  (-130.3,89)  [p=0.3] | +4  (109.4,117)  [p=0.8] |
| HOMA IR | 6.6  (4.7) | 5.2  (3.2) | 7.4  (3.8) | -1.4  (-4.8,2) | +0.8  (-3.1,4.7) |
| **Insulin (AUC)(pmol/l)** | 3387  (2417) | 2173  (1845) | 2780  (2588) | -1214 (3034,606)  [p=0.05] \* | -607  (-2835,1621)  [p=0.4] |
| ALT | 47.3  (25.6) | 43  (23.8) | 48.8  (28.7) | -4.3  (-25.2, 16.6)  [p=0.4] | +1.5  (-22.7, 25.7)  [p=0.7] |
| Gamma GT | 32.9  (13.1) | 25.8  (9.5) | 29.4  (12.5) | -7.1  (-16.8, 2.6)  [p=0.03] \* | -3.5  (-15,8)  [p=0.3] |
| Cholesterol | 4.4  (0.7) | 4.1  (0.6) | 4.3  (0.8) | -0.3  (-0.85,0.25)  [p=0.2] | -0.1  (-0.8,0.6)  [p=0.4] |
| Triglycerides | 1.5  (0.7) | 1.9  (0.8) | 1.3  (0.6) | +0.4  (-0.24,1.04)  [p=0.1] | -0.2  (-0.8,0.4)  [p=0.4] |
| **HBA1c**  **(mmol/mol)** | 36.2  (2.5) | 35.1  (1.8) | 34.1  (2) | -1.1  (-2.9,0.7)  [p=0.08] | -2.1  (-4.1, -0.1)  [p=0.005] \* |

### Incretins, Adipokines and Ghrelin

We also measured the incretins GLP-1 and GIP during the OGTT at the same time points –baseline, 6 months at balloon removal and further 18 month follow up (See table 25).

Table 26 - Mean GLP-1 at baseline, 6 months at balloon removal and further 24 month follow up (in pmol/l)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **GLP-1**  **0min** | **GLP-1**  **30 min** | **GLP-1 60min** | **GLP-1 90min** | **GLP-1**  **120min** |
| **Baseline Mean** | **1. 8** | 3. 8 | 2. 5 | **2** | 2. 6 |
| **Baseline SD** | 2. 3 | 2. 9 | 3. 2 | 1. 3 | 2. 3 |
| **6 mth**  **Mean** | 3.6 | 4.1 | 3.6 | 3.6 | 3.3 |
| **6 mth**  **SD** | 5.7 | 5.9 | 5.3 | 4.8 | 5.1 |
| **24 mth**  **Mean** | **2.9** | 4.1 | 3.5 | **3.6** | 3.1 |
| **24 month**  **SD** | 1.8 | 2.6 | 2.1 | 1.8 | 1.4 |
| **p value 0-6** | 0.15 | 0.87 | 0.29 | 0.86 | 0.62 |
| **P value 0-24** | 0.04\* | 0.21 | 0.24 | 0.04\* | 0.07 |

GLP-1 levels peaked at 30 minutes during the OGTT at all 3 time points: baseline, at balloon removal at 6 months and at 24 months.

There was a significant increase in fasting GLP-1 over the 24 months (p=0. 04). This was also seen at 90 minutes.

The figure 29 below shows the mean GLP-1 during the OGTT at baseline, 6 months and 24 months.

Figure 31 -Mean GLP-1 at baseline, 6 months and 24 months during an OGTT with measurements at 0,30,60,90 and 120 minutes

GLP-1 AUC using the trapezoid method increased from 10.9±10.1 pmol/l to 14.4±21 (p=0.44) and remained above baseline at 24 months (13.9±7) (p=0.15).

despite weight regain.

Table 27 - Mean GIP at baseline, 6 months at balloon removal and further 24 month follow up (in pg/mll)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **FigureFigure** | **GIP**  **0min** | **GIP**  **30 min** | **GIP**  **60min** | **GIP**  **90min** | **GIP**  **120min** |
| **BaselineMean** | 34. 4 | **224. 7** | **244. 5** | **242. 2** | **183. 1** |
| **Baseline SD** | 16. 6 | 80. 3 | 78. 9 | 66. 6 | 76. 6 |
| **6 month Mean** | 25.3 | **119.2** | **93.3** | **93.1** | **104.3** |
| **6 month SD** | 14.8 | 53.4 | 50.8 | 34.9 | 33.8 |
| **24 month Mean** | 70.6 | 244.2 | 241.4 | 258.4 | 238.1 |
| **24 month**  **SD** | 50.9 | 106.5 | 100.9 | 91.9 | 81.6 |
| **P value 0-6** | 0.2 | 0.002\* | 0.0005\* | 0.0002\* | 0.005\* |
| **P value 0-24** | 0.1 | 0.62 | 0.63 | 0.64 | 0.17 |

There was a significant decrease in GIP secretion throughout the OGTT (at 30,60,90 and 120 minutes) at 6 months at balloon removal after the weight loss though fasting levels were not different.

The significant drop in AUC GIP at 6 months (P<0. 00001) was not sustained at 24 months. Figure 30 shows the mean GIP during the OGTT at baseline, 6 months and 24 months.

Figure 32 - Mean GIP at baseline, 6 and 24 months during an OGTT

We noted moderately strong inverse correlations between percentage weight loss and change in GLP-1 AUC (r=-0. 45) and ghrelin (r=-0. 51) at 6 months.

**Adipokines**

There was no significant change in fasting ghrelin values, leptin and adiponectin at the 3 time points.

Table 28 - Ghrelin, leptin and adiponectin at baseline, 6 months and 24 months

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **Ghrelin (pg/ml)** | | | | **Adiponectin ng/ml** | | | **Leptin ng/ml** | | |
|  | **Baseline** | | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 441 | 475 | | 469 | 7. 5 | 5. 4 | 8. 8 | 35. 9 | 36. 5 | 24. 7 |
| **BOB02** | 222 | 225 | | 547 | 5. 9 | 4. 5 | 5. 1 | 37 | 28 | 28. 9 |
| **BOB03** | 111 | 87 | | 134 | 15. 2 | 10. 5 | 9. 8 | 28. 9 | 33 | 29. 3 |
| **BOB04** | 131 | 212 | | 114 | 10. 4 | 9. 8 | 9. 9 | 34. 7 | 22. 2 | 15. 6 |
| **BOB05** | 186 |  | | 202 | 8. 8 |  | 5. 1 | 31. 1 |  | 25. 5 |
| **BOB06** | 242 | 267 | | 151 | 18. 1 | 20. 5 | 16. 5 | 25 | 26. 5 | 25. 6 |
| **BOB07** | 230 | 333 | | 288 | 16. 9 | 13. 6 | 15. 2 | 34. 7 | 24. 1 | 27. 8 |
| **BOB08** | 196 | 250 | | 159 | 16. 2 | 12. 5 | 9. 8 | 34. 8 | 33. 7 | 40. 9 |
| **BOB09** | 340 | 114 | |  | 11. 8 | 3. 6 |  | 28. 2 | 29. 5 |  |
| **BOB10** | 61 | 11 | | 68 | 13. 6 | 16. 2 | 28. 2 | 40. 5 | 26. 7 | 34. 5 |
| **BOB11** | 173 | 165 | | 131 | 24. 4 | 28. 6 | 18. 4 | 32 | 30. 3 | 34. 1 |
| **BOB12** | 328 | 319 | |  | 20. 2 | 25 |  | 27. 2 | 29. 8 |  |
| **Mean** | 221. 6 | 223. 4 | | 226. 3 | 14. 1 | 13. 7 | 12. 7 | 32. 5 | 29. 1 | 28. 7 |
| **SD** | 106. 4 | 128. 9 | | 160. 4 | 5. 5 | 8. 3 | 7. 1 | 4. 6 | 4. 2 | 6. 8 |
| **P 0-6** | 0.95 |  | |  |  |  |  |  |  |  |
| **P 0-24** | 0.46 |  | |  |  |  |  |  |  |  |

Table 29 - Table outlines the change in GLP-1 AUC, GIP AUC, fasting GLP-1, fasting GIP, Leptin, Adiponectin and Ghrelin between baseline, balloon removal at 6 months and 2 years (18 months after balloon removal)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Before Balloon insertion**  **N=12**  **Mean (±SDs)** | **At 6 months after Balloon removal**  **N=12**  **Mean ((±SDs)**  **[P value]** | **At 2 years-18 months post balloon removal**  **N=10**  **Mean ((±SDs)**  **[P value]** | **Mean difference between baseline and balloon removal at 6 months**  **(95 CI)** | **Mean difference between baseline and**  **24months**  **(95 CI)** |
| GLP-1 AUC (pmol/l) | 7. 5  (5. 3) | 8. 5  (5. 7)  [p=0. 7] | 14. 8  (6. 8)  [p=0. 05] | +1. 0  (-3. 8,5. 8) | +7. 3  (1. 9,12. 7) |
| GIP AUC  (pg/ml) | 817. 4 (143. 1) | 364. 8  (108. 7)  [p=0. 00001] \* | 960. 3  (272. 6)  p=0. 1] | -452. 6  (-563. 6, -341. 6) | +142. 9  (-45. 9,331. 7) |
| Fasting GLP-1  (pmol/l) | 1. 8  (2. 3) | 3. 6(5. 7)  [p=0. 2] | 2. 9(1. 8)  [p=0. 04]\* | +1. 8  (-1. 9,5. 5) | +1. 1  (-0. 8,3) |
| Fasting GIP  (pg/ml) | 34. 3  (16. 6) | 25. 3  (14. 8)  [p=0. 2] | 70. 6  (58. 9)  [p=0. 1] | -9. 0  (-22. 7,4. 7) | +36. 3  (-0. 7,73. 3) |
| Leptin  (ng/ml) | 32. 5  (4. 6) | 29. 1  (4. 2)  [p=0. 1] | 28. 7  (6. 8)  [p=0. 07] | -3. 4  (-7. 2,0. 4) | -3. 8  (-8. 9,1. 3) |
| Adiponectin (ng/ml) | 14. 1  (5. 5) | 13. 7  (8. 3)  [p=0. 5] | 12. 7  (7. 1)  [p=0. 6] | -0. 4  (-6. 5,5. 7) | -1. 4  (-7,4. 2) |
| Ghrelin  (pg/ml) | 221. 8  (106. 4) | 223. 5  (128. 9)  [p=0. 9] | 226. 3  (160)  [p=0. 5] | +1. 7  (-100. 4,103. 8) | +4. 5  (-114. 5,123. 5) |

There was a strong moderate (r=0. 51, p=0.05) negative correlation between percentage weight loss and ghrelin.

### Discussion

#### Weight loss

The weight loss was variable, the reasons for which are still unclear. Young people in our study lost 7 kg on average with a range of -23 kg to +2 kg. This equated to an average weight loss of 5% across the group. Weight loss of 5-7 % is oft quoted as clinically significant -the amount needed to experience health benefits (71). A mean BMI SDS change of 0.2 is considered significant in bringing about changes in metabolic parameters in previous studies and the young people in our study experienced this. Certainly, in recent studies relating to balloons in adolescents (older, less obese compared to our cohort), weight loss far exceeded our experience with a BMI change of 5. 86. (100).

Even for those with minimal weight loss, or some weight gain, an examination of the weight trajectory over the previous years showed that this was a positive outcome. The young people had experienced a mean weight gain of 11 kg in the year prior to enrolling on the project. Data was available for atleast 2 years before the start of the project and the natural history was similar, with unremitting weight gain.

The reason for the weight loss perhaps not being as expected may be manifold.

Engagement with the lifestyle intervention of the project was variable. A total of 38 visits were planned before the balloon went in and till 8 weeks after balloon removal. An average of 13.7 (7. 8) number of visits took place. The numbers are few but there was a correlation (r=0. 57 for visits to the exercise officer and r=0. 36 for visits made to the doctor) between numbers of sessions attended and weight loss experienced. A retrospective intragastric balloon study with 27 adolescents (23 female) also found a similar correlation between the weight loss experienced and the adherence to the multidisciplinary programme (r=0.53, p=0.005). (100). Though, in our study, home visits were planned, there was no enthusiasm for these and only a few visits took place. It is difficult to say whether frequent attendance helped or whether the frequent attendance reflected motivation.

Engagement with hospital visits to see the doctor was much better, perhaps a medical appointment was perceived as more important by the families or perhaps medical teams have a more didactic approach in getting patients to attend.

The dietetic focus was on a healthy diet with reduced portions rather than restriction to a certain number of calories because of concerns about growth. However, given that these young people were Tanner stage 4/5, and had completed most of their growth, more stringent criteria could have been adopted. Dietetic input was provided at balloon insertion and removal with the message reinforced by the exercise and science officer. More consistent and regular dietetic input would perhaps have made it easier for participants to stick to a calorie controlled diet.

#### Waist and hip circumference.

Waist circumference decreased significantly with decrease in weight over the 6 months. However, the mean still stayed well above the 99. 6th centile for age and gender. It then increased again at 24 months to above baseline.

Waist circumference is considered a proxy measure for central adiposity.

In our study, the change in waist circumference showed a correlation with change in HBA1c and AUC for insulin over the 1st 6 months (r=0.38 and r=0.33 respectively) when majority of the weight loss occurred. There was a correlation between change in waist circumference and diastolic blood pressure following weight loss at 6 months (r=0.56).

There was a correlation between the reduced waist circumference at 6 months and reduced cholesterol at 24 months (the cholesterol fell even with weight gain) suggesting possible longer term benefit of weight loss (r=0.46) perhaps reflecting healthier choices.

A cross sectional study from the NHANES data base (n=2155, 6-19 years olds) has previously shown that waist circumference has a stronger association with cardio metabolic risk compared to BMI z scores(287). In adults it has been shown that for a certain waist circumference, people had the same obesity related health risk irrespective of whether they were normal weight, overweight or obese. (288)

However, the ALSPCA study from Bristol showed that BMI alone can help identify children at risk of cardiovascular disease (defined by changes in risk factors like blood pressure, LDL, Triglycerides and HDL, fasting insulin/glucose ratio) and that measures of abdominal obesity may not necessarily add to this(289). It also showed that if overweight and obese girls at age 9-12, lost weight by 15-16 years, their cardiovascular risk profile was the same as the 9-12-year-old girls with normal weight. However, in boys, the risk was beween those overweight at both ages and normal weight at both ages.

A more recent prospective study –the HEALTHY trial in a multi-ethnic cohort of >4000 children in America over two and half years follow up (6th and 8th grade)| showed that while change in BMI may have a stronger association (fasting triglycerides, cholesterol, systolic and diastolic blood pressure and fasting glucose), change in waist circumference can be an indicator of high fasting glucose which is significant in the development of type 2 diabetes(290).

Our study has shown a significant drop in waist circumference at 6 months accompanied by a significant change in BMI SDS which correlated weakly with markers of insulin glucose metabolism (HOMA and HBA1c) but more strongly with change in diastolic blood pressure.

#### Blood pressure

Systolic, diastolic and mean blood pressures were all lower (non-significantly) at 6 months after weight loss following balloon removal.

In studies looking at impact of weight loss on blood pressure in adults followed up for 6 years, showed that there was a progressive drop in systolic and diastolic BP initially (up till 13 % weight loss) but then seemed to plateau. (291). In our study, the decrease in waist circumference at 6 months was associated with drop in Diastolic blood pressure and the improvement in diastolic blood pressure persisted despite the weight regain. The UKPDS Blood pressure control trial did show reduced complications but no significant difference between the intervention and control groups (tight and less tight control of blood pressure ) suggesting that the metabolic memory aspect may not apply to all the different comorbidities and that tight control needs to be maintained for sustained benefit(292).

#### Glucose and insulin metabolism

The young people in the study experienced a BMI SDS reduction of 0.2 with BMI change of 2.5 kg/m2. Certainly, in adult’s 5-10 percent weight loss is quoted to bring about cardiovascular benefit and while this is also known in children, very few studies have quantified this in the same way. The BMI SDs change in our study was like that seen in many life style programmes, (663 obese children aged 4-16 years, BMI SDS change 0.36)(293) though the level of obesity was much higher in our study and more keeping in with bariatric populations. Younger children did better suggesting interventions need to be put in earlier.

Despite a BMI mean of 47, none of the young people in our study had impaired glucose tolerance or type 2 diabetes.   
Peak insulin levels, fasting insulin and HOMA-IR were high suggesting insulin resistance.  
At 6 months with weight loss, there was a significant reduction in AUC for insulin as well as mean insulin at 90 minutes. Fasting insulin was 21 points lower at 6 months though this did not reach significance. Fasting glucose was significantly lower at 60 minutes.   
Peak insulin reached was also significantly lower (p=0.006).   
HBA1c dropped at 6 months and continued to improve significantly at 2 years after weight gain. Weight loss was correlated with AUC insulin and HBA1c at 6 months and this correlation was stronger at 24 months (p=0.04). This suggests the possible impact of metabolic memory and that the weight loss had a potential future benefit on HBA1c despite weight regain. This was a pilot study and not powered for multiple end points.

We discussed the significant drop in HBA1c within the study team and the consensus was that the error should be consistent over the two years as our expectation is that errors would be randomly distributed.

The Diabetes Control and Complications Trial included almost 1500 subjects with type 1 diabetes randomly assigned to conventional or intensive groups for 6.5 years and 93 percent of them were followed up for a further 30 years through the Epidemiology of Diabetes Interventions and Complications Study (EDIC). They found that intensive therapy (HBA1C of 53 mmol/mol versus HBA1c of 75 mmol/mol) reduced the incidence of cardiovascular disease by 30 % (95% CI 7,48; p=0.016) and major cardiovascular events by 32%(95%CI -3,56; p=0.07). This benefit persisted even if the HBA1c subsequently became higher(294).

Our young cohort did not have type 2 diabetes, though most had Insulin resistance and given their weight trajectory were at high risk to develop T2DM.

Good glycemic control over a period has longer term benefits alongside the immediate; this is known as ‘metabolic memory’. It is not clear how long this would last, however, there is reason to try and spend more time in target as much as possible. (295)

Though EDIC was based on T1DM, this was also shown in the UK PDS trial for type 2 patients and can be extrapolated especially since the cardiovascular risk is so high.

Even a small BMI SDS change of 0.1 following a public health nurse combined with hospital treatment programme (307 children between 7-17 years) in the Oslo Adiposity Intervention Study was shown to bring about improvements in cholesterol, LDL, insulin and HOMA-IR at similar levels as seen in our study. (296) This is important as even small changes in insulin and insulin resistance can have an impact on cardiovascular risk and that of diabetes in the longer term(297).

Another study looking at what reduction in BMI SDS is needed in obese adolescents (88, 40 boys, median age 12.4 years, mean BMI SDS 3.23) to bring about meaningful change in body composition and cardio metabolic health showed that a reduction of ≥ 0.25 improved insulin sensitivity, blood pressure and total cholesterol/high density lipoprotein ratio.(298)

Changes in glucose insulin metabolism seen in our study are like changes described in life style intervention programmes where the change in BMI SDS was comparable.

#### Lipid Profiles

In our cohort, cholesterol levels reduced at 6 months (-0.27 (-0.85, 0.25, p=0.2) and rose again but still stayed below intervention levels at 24 months following weight regain.

Triglycerides rose at 6 months (0.4(-0.24, 1.04, p=0.1) but fell at 24 months (-0.2(-0.8,0.4) p=0.4).

There was no change in the number of YP with dyslipidemia even though this may have been expected based on the 5 percent weight loss and BMI SDS change of 0.2 as discussed above.

#### Liver enzymes

ALT fell as did Gamma GT (significantly) at 6 months following weight loss. Gamma GT stayed below pre-intervention levels at 24 months despite weight gain. Though 5/12 had elevated ALT, only 2 were clinically significant.

Prevalence of NAFLD in childhood obesity is quoted as high as 40 percent in some studies(299) and higher (50%) in those who consume even modest amounts of alcohol . This can then progress onto cirrhosis in some cases. The prevalence of raised liver enzymes is about 10 percent in obese YP and several noninvasive techniques are being proposed to help evaluate those who need a liver biopsy as NAFLD can be present even in the absence of raised transaminases.

Unfortunately, we did not carry out liver ultrasound scans in our cohort of YP.

#### Vitamins, minerals and iron

Several young people in our study had suboptimal Vitamin D levels. Vitamin D deficiency is known to be common in obesity due to diet inadequate in Vitamin D (even though over all calorie intake is high), sedentary lifestyles and sequestration of fat soluble vitamin in the increased amount of adipose tissue(300). Our incidence is similar to other cohorts of severely obese young people where >1/3rd of participants had vitamin D deficiency(73) and levels remained the same at 3 year follow up post bariatric surgery.

In our cohort, the young people were encouraged to take a multivitamin each day and at 2 years only one had Vitamin D levels <25 ng/ml. (5 at baseline and 3 at 6 months). This is important as the Vitamin D deficiency in obesity with the related secondary hyperparathyroidism is postulated to be one of the mechanisms of bone loss, though there are studies showing that an independent relationship exists as well(301). A key message from our study would therefore be to check for Vitamin D deficiency in severe obesity and to treat this rigorously.

Unfortunately, there was a problem with our PTH assay at the start of the study which affected some of our participants and meant that baseline results were not reliable, hence we decided not to measure it at 6 and 24 months.

In a cohort of young people undergoing bariatric surgery (Teen LABS), deficiencies in Vitamin A level were 6 percent before the procedure and increased to 16 percent after. Our cohort of YP had normal vitamin A levels.

Iron deficiency anemia was documented in only one of our cohort. This improved over the 2 years and she was no longer anemic. Hypoferritinemia was a significant concern in the post bariatric surgery follow up in the cohort described above as it increased from 5 percent at baseline to 57 percent at 3 years’ post operatively.

#### Summary

Overall, the young people in our study experienced clinically significant weight loss with change in some weight related co-morbidities. However, only some of these benefits were sustained longer term.

In a 3 year follow up of adolescent who underwent bariatric surgery (242 adolescents, bypass 161 and sleeve 67, mean BMI 53) who experienced a mean weight loss of 27%, upto three quarters had normalized their blood pressure on follow up. Remission of diabetes was seen in 95 percent, abnormal kidney function normalized in 86 %, prediabetes remission in 76 percent and remission of dyslipidemia in 2/3rds of those who had this at baseline. In this cohort, 96 had elevated BP, 171 had dyslipidemia and 29 had diabetes. These results suggest better co-morbidity resolution than that seen in adults suggesting that adolescents maybe able to reverse the cardio metabolic consequences of obesity better.

They also noted development of elevated BP (4), dyslipidemia (3), abnormal KFT (12) in cases who had not had this at baseline. (73)

The amount of weight loss was far more than what our young people experienced as was the co-morbidity resolution. In a systematic review looking at metabolic outcomes following intragastric balloon therapy (5668 subjects, 10 RCT’s and 30 observational studies) lower comorbidity resolution (odds ratio of diabetes resolution was 1.4, mean fasting glucose, diastolic BP, waist circumference and triglycerides were all lower) was seen in adults in comparison to what is described above(302).

In our study, benefit in diastolic blood pressure, insulin area under the curve and HBA1c were maintained at 2 years despite weight regain.

Another systematic review of bariatric surgery in adolescents which included follow up of at least 5 year follow up with 70 percent retention rate (10 studies) showed a mean BMI at baseline and follow up of 47 and 32.4 kg/m2 respectively. Weight regain was seen between 1-12 years of follow up and the conclusion was that there is low to moderate evidence regarding reduction in BMI and very low to low evidence related to resolution of co-morbidity.(303)

The intra-gastric balloon is therefore unlikely to deliver the kind of weight loss seen after bariatric surgery. Weight loss and co-morbidity resolution is only slightly better than that seen after life style interventions. This was a motivated group who had failed life style intervention previously (except BOB12 and BOB07 who had lost some weight and then plateaued)

IGB will continue to play a role for those whom life style intervention is not enough but a permanent surgical procedure is not appropriate.

#### Incretins, adipokines and ghrelin

Adipose tissue synthesizes and secretes many peptides (adipokines) that are involved in the regulation of energy homeostasis, insulin action and lipid metabolism(304). Adiponectin is the most abundant protein secreted by adipose tissue and circulates in lower concentrations in obesity and insulin resistant states(305) . Circulating levels are known to increase after weight loss, with large losses of body weight from bariatric surgery leading to significant increases while moderate weight loss from caloric restriction not resulting in any change in levels(306, 307). We demonstrated no significant change in levels of adiponectin consistent with other studies where overall weight loss is modest. However, there were nevertheless improvements in insulin sensitivity. Recent data suggest that adiponectin is a mediator of insulin sensitivity(308)and that high levels protect against development of Type 2 diabetes(309) . In the Faraj study of 50 morbidly obese adults who underwent RYGB, adiponectin increased significantly (50.1%±47, p<0.001) and the best predictor of improved post operative insulin sensitivity was the increase in adiponectin (r=0.7, p=0.01). Our data suggest perhaps not unsurprisingly that it is not the only mediator of change in insulin sensitivity.

Leptin secretion is dependent on fat mass and studies show strong correlations between leptin concentration change and change in BMI and insulin concentration and resistance following weight loss(310). We also noted a moderate correlation with change in insulin production during the OGTT (insulin at 0 (r=-0.68, p=0.03) and 30 minutes (r=-0.72, p=0.03) and change in Leptin at 6 months.

Ghrelin is the only satiety hormone known to be linked to feeding behavior, being highest before a meal and low after. It is postulated that this postprandial inhibition may be missing in obesity resulting in a continued desire to eat. It is unclear what happens to ghrelin after weight loss though some studies suggest it is inversely related to weight. Some studies have shown increased fasting ghrelin after banding or diet induced weight loss and decreased after sleeve gastrectomy or bypass that could be related to the change in anatomy seen in these procedures(311).

Some studies do suggest that weight loss associated with the balloon could be mediated by the appetite regulating hormones. In a study of 66 adults with metabolic syndrome who were randomized to 6 month IGB with a 12 month behavorial intervention programme versus a 12 month behavorial intervention programme alone, ghrelin increased while leptin decreased when the intragastric balloon was in situ and both returned to baseline after its removal. Significant weight loss was seen in the balloon group. We did not measure Adipokines or ghrelin while the balloon was still in situ at the end of the 6 months which may have shown a mechanical impact of having the balloon in situ. No changes were seen in adiponectin and no change was seen in ghrelin levels a year after the initial weight reduction(312).

We demonstrated no significant change in ghrelin levels before or after the balloon. But subsequent weight regain after balloon removal showed a strong correlation (24-month weight change) with change in ghrelin levels (-0. 89, p=0.009). This raises the possibility that Ghrelin may be a predictor of success or otherwise for individuals with intragastric balloons.

Enterokines, particularly incretins such as, Glucagon like Peptide (GLP-1) and Glucose dependent Insulinotrophic Peptide (GIP) are released from the gut in response to a nutrient challenge and lead to a glucose dependent insulin release from the pancreas. The “Incretin Effect” describes the phenomenon whereby a glucose load delivered orally produces much greater insulin secretion than the same glucose load administered intravenously. The incretin effect is impaired in type 2 diabetes in adults upto 50-70 per cent due to decreased secretion of GLP-1 and a reduced effect of GIP.

Effect on GLP-1 of weight loss due to hypocaloric diets is inconsistent(313) but levels are known to increase after gastric bypass(314). Peak levels are usually maintained in healthy participants but reduced to lower levels in diabetics. However, post certain types of bariatric surgery (gastric bypass and biliopancreatic diversion), remission of type 2 diabetes is seen even before the effects of the weight loss have set in and this is thought to be due to the change in the secretion of gastrointestinal hormones including the incretin GLP-1(315).

There is little data about incretins in adolescents. A recent study in obese Korean adolescents suggests that there is no difference in GLP-1 and GIP levels in obese adolescents with and without newly diagnosed diabetes. There were 12 adolescents in each group, mean age 13.8±2 years, BMI SDS 2.1±0.5, abd insulin, c peptide, insulinogenic index and HOMA-Beta cell function were all significantly lower in the T2DM group. (316).

We demonstrated a non-significant increase in GLP-1 AUC that correlated well with degree of weight loss at 6 months (-0. 45, p=0.05). The benefit was retained with both fasting GLP-1 and 90 minute GLP-1 (p<0. 04) and GLP-1 AUC improved (p<0. 06) at 24 months despite weight regain (just reaching significance).

Decrease in post prandial GIP has been noted in adolescents after RYGB (more pronounced in those with diabetes than non-diabetics). The postprandial reduction is evident in advance of weight loss, with reports on the effect on fasting GIP being less consistent. Most human studies do show a reduction in GIP following malabsorptive procedures(122).

In our study, stimulated GIP at 6 months showed a significant decrease at all time points (30,60,90 and 120). It suggests that there maybe a degree of GIP resistance secondary to obesity, which improved after weight loss, and reestablished following weight regain.

We did not see any significant correlations between the changes in incretins and bone turnover markers or measures of body composition and bone microarchitecture.

Our numbers are too few to confirm any associations but certainly show an impact on the incretin effect following weight loss. Larger, adequately powered studies are needed to study this in more detail in obese adolescents and following interventions leading to weight loss-both diet and exercise induced where changes in the gut anatomy do not play a role as well as in bariatric procedures-both restrictive and malabsorptive as both the weight loss and the weight loss mechanisms are likely to play a role.

## DXA, HRpQCT, Bone turnover markers

One of the worries regarding rapid and significant weight loss in young people is the impact of this on skeletal health at the time of peak bone mass accrual, a process which continues till at least 25 years of age. This next chapter will cover the results and discussion regarding changes in DXA and HRpQCT at 6 months and 24 months. It also includes changes in bone markers (bone formation and resorption) and any significant correlation with change in bone density and microarchitecture and strength.

### DEXA

All 12 participants had their baseline DXA. The first scan was on average 4 weeks before balloon insertion, the second within 8 weeks of balloon removal and the last scan was on average at 25 months (SD 2.2) after the first.

Eleven had their 6 month DEXA (BOB05 did not come for follow up despite multiple attempts).

Ten had their 24 month follow up (BOB09 did not come despite multiple attempts, BOB12 withdrew from the study due to a prolonged psychotic episode).

There was no significant change in height over the period and no fractures were sustained during the follow up period.

Change in DXA parameters between visits are described in the tables below with significant changes (p<0.05) highlighted with asterix. We also calculated percentage change from baseline.

#### Change from Visit 1 to Visit 2

Table 30 - DXA Data – Change from visit 1 to visit 2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 2**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **% change** |
| TBLH BMD  (g/cm2) | 11 | 1. 15  (0. 08) | 1. 15  (0. 06) | 0. 002  (-0. 03, 0. 03) | 0. 853 | 0.1 |
| TBLH BA  (cm2) | 11 | 2010. 2  (240. 7) | 2056. 5  (205. 3) | 46. 4  (-15. 8, 108. 5) | 0. 127 | 2.3 |
| TBLH BMC  (gms) | 11 | 2307. 9  (287. 6) | 2368. 6  (254. 1) | 60. 7  (5. 5, 115. 9) | 0. 034\* | 2.6 |
| L1-L4 BMD  (gm/cm2) | 10 | 1. 23  (0. 15) | 1. 26  (0. 16) | 0. 03  (0. 01, 0. 04) | 0. 007\* | 2.4 |
| L1-L4 BA  (cm2) | 10 | 57. 4  (7. 6) | 58. 1  (7. 5) | 0. 8  (0. 4, 1. 2) | 0. 002\* | 1.4 |
| L1-L4 BMC  (gm) | 10 | 70. 5  (13. 0) | 73. 0  (13. 3) | 2. 5  (1. 4, 3. 6) | 0. 001\* | 3.5 |
| TBLH Fat Mass  (gm) | 10 | 68014  (14265) | 63468  (15113) | -4546  (-19142, 1948) | 0. 099 | -6.7 |
| Truncal Fat Mass(gm) | 10 | 38046  (9916) | 33544  (8659) | -4501  (-8565, -437) | 0. 033\* | -11.8 |
| TBLH Lean Mass (gm) | 10 | 57281  (10303) | 57484  (10715) | 203  (-1456, 1862) | 0. 788 | 0.35 |
| TBLH Fat Mass % | 10 | 54. 2  (3. 3) | 52. 2  (5. 0) | -2. 0  (-3. 9, -0. 03) | 0. 047\* | -3.7 |
| % Truncal Fat Mass | 11 | 56. 7  (3. 2) | 54. 6  (5. 3) | -2. 1  (-4. 0, -0. 1) | 0. 038\* | -3.7 |

Despite 5.1 (4.8) percent weight loss, (due to a 6.7 percent reduction in TBLH Fat Mass (p=0.0001, r=0.97) and an almost 12 percent reduction in Truncal Fat mass (p=0.007, r=0.75)), the Total Body Less Head (TBLH) Bone Mineral Content (BMC)(60.7(5.5,115.9, p=0.034), L1-L4 Bone Mineral Density (BMD)(0.03(0.01,0.04),p=0.007), Bone Area (BA)(0.8(0.4,1.2),p=0.002)and Bone Mineral content (BMC)(2.5(1.4,3.6), p=0.001) all increased at 6 months at balloon removal.

There was a significant negative correlation between change in truncal fat mass and L1-L4 BMD (r=-0.77, p=0.009) and BMC (r=-0.77, p=0.008).

The figures 32 and 33 below describe the changes in the DXA measures (TBLH FM, LM, Truncal FM, TBLH BMD, TBLH BA, TBML BMC, L1-L4 BMD, L1-L4 BA and L1-L4 BMC. between visit 1 and visit 2 (\* signify significant change)

Figure 33 - Changes in fat mass, truncal fat mass, lean mass between visit 1 and visit 2 (Circles represent the mean and lines represent the 95% confidence intervals)

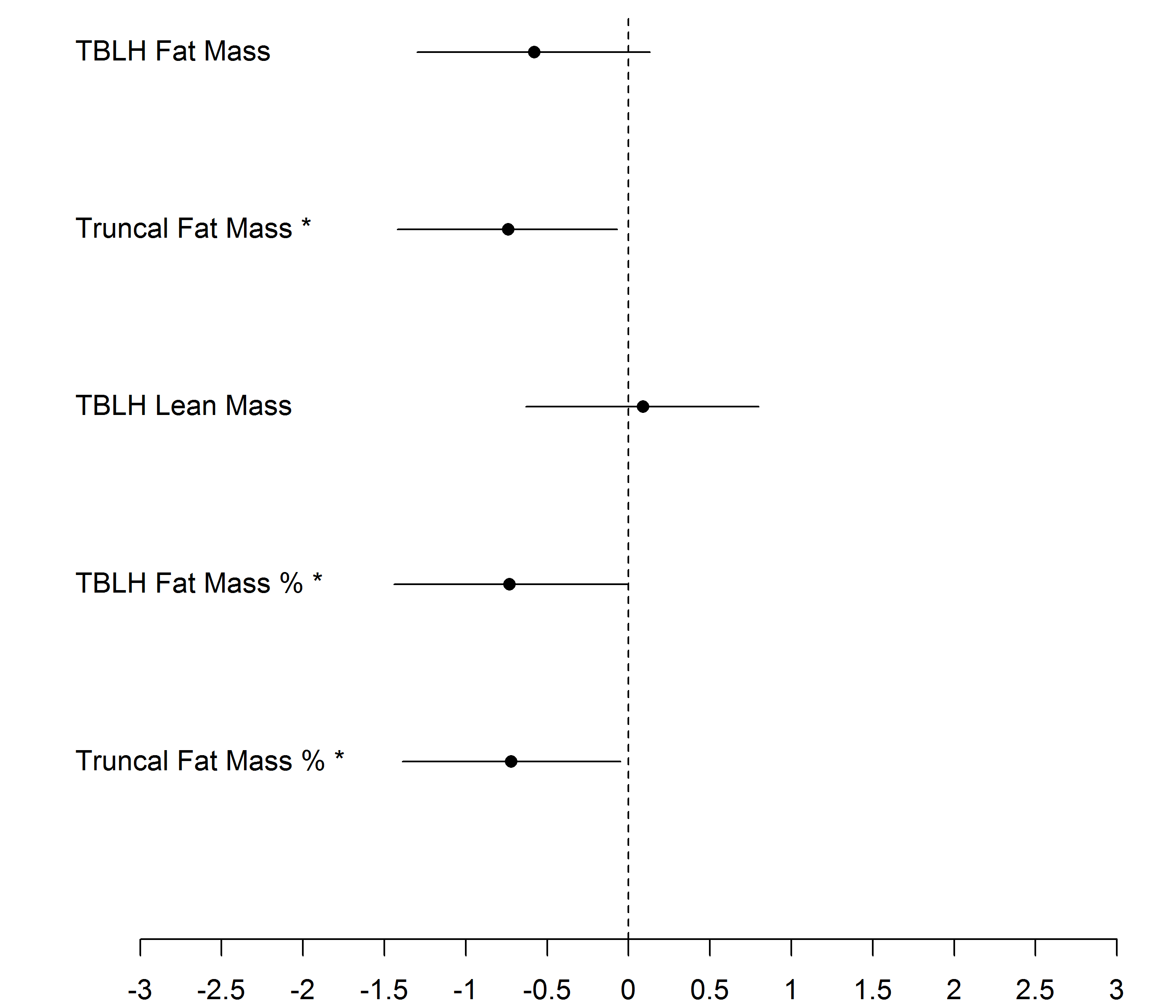
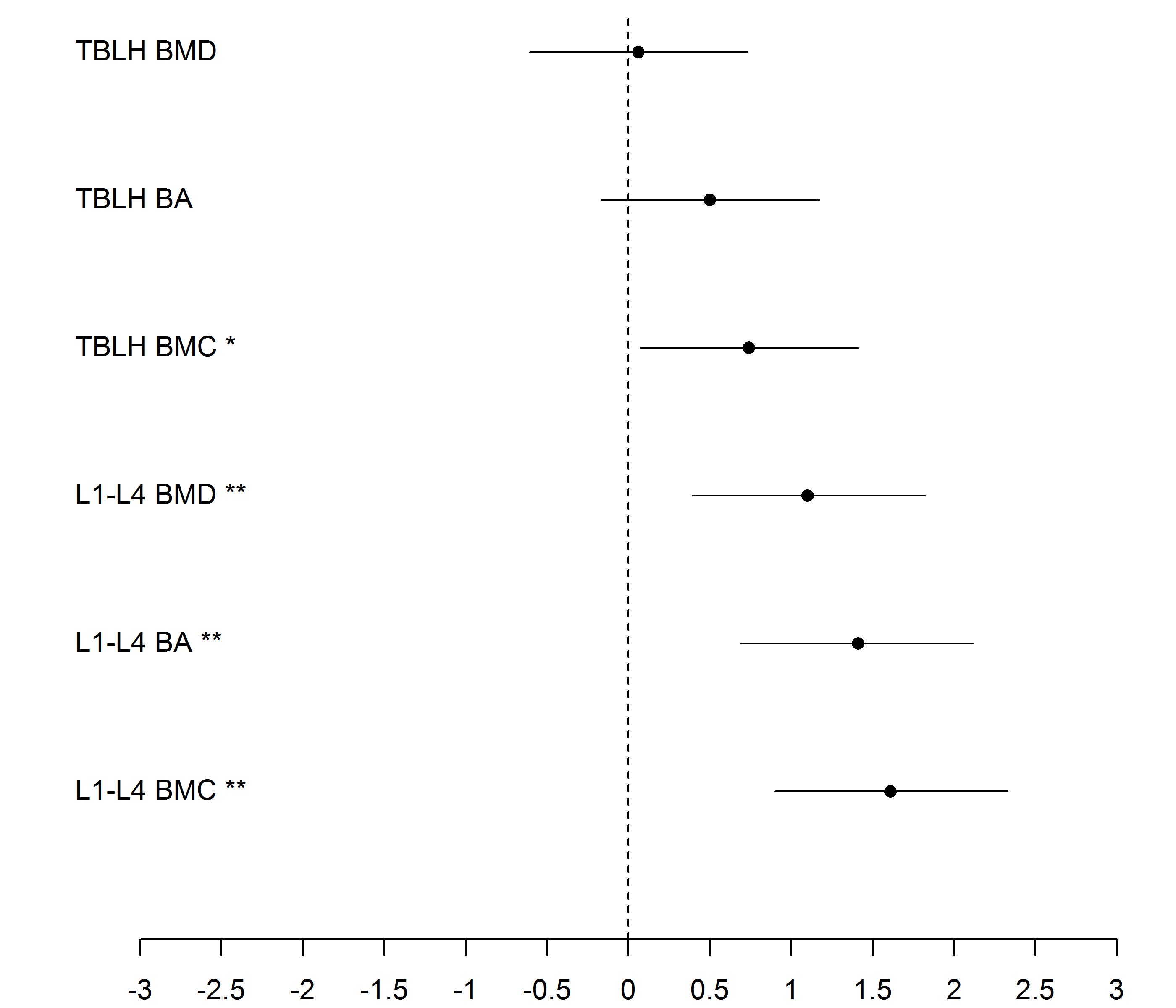


Figure 34 - Change in TBLH BMD, TBLH BA, TBLH BMC, L1-L4 BMD, L1-L4 BA, L1-L4 BMC in patients between visits 1 &2



#### Change from Visit 2 to Visit 3

The next table describes the changes between visit 2 and 3 when most of the participants regained weight.

Table 31 - DXA Data – Change from visit 2 to visit 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 2**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **% change** |
| TBLH BMD (gm/cm2) | 9 | 1. 16  (0. 06) | 1. 20  (0. 09) | 0. 04  (0. 02, 0. 06) | 0. 004\* | 3.5 |
| TBLH BA  (cm2) | 9 | 2038. 4  (206. 1) | 1981. 2  (256. 8) | -57. 2  (-113. 1, -1. 3) | 0. 046\* | -2.8 |
| TBLH BMC  (gm) | 9 | 2362. 6  (276. 6) | 2363. 2  (348. 9) | 0. 6  (-68. 7, 69. 9) | 0. 985 | 0.02 |
| L1-L4 BMD  (gm/cm2) | 9 | 1. 28  (0. 05) | 1. 30  (0. 06) | 0. 02  (-0. 02, 0. 07) | 0. 329 | 1.5 |
| L1-L4 BA  (cm2) | 9 | 58. 5  (7. 3) | 59. 5  (7. 5) | 1. 0  (0. 1, 2. 0) | 0. 041\* | 1.7 |
| L1-L4 BMC  (gm) | 9 | 74. 5  (13. 2) | 77. 3  (15. 3) | 2. 8  (-0. 5, 6. 0) | 0. 084 | 3.8 |
| TBLH Fat Mass  (gm) | 9 | 66817  (14230) | 74544  (19868) | 7726  (-2112, 17564) | 0. 108 | 11.5 |
| Truncal Fat Mass  (gm) | - | - | - | - | - |  |
| TBLH Lean Mass  (gm) | 9 | 56990  (11634) | 59899  (9392) | 2909  (290, 5528) | 0. 034\* | 5.1 |
| TBLH Fat Mass % | 9 | 53. 9  (5. 1) | 54. 8  (7. 9) | 0. 9  (-2. 0, 3. 8) | 0. 504 | 1.7 |
| Truncal Fat Mass% | - | - | - | - | - |  |

Weight increased significantly between visit 2 and visit 3 (12.9% weight change between the 2 visits but 7.2% increase from baseline).

TBLH BMD (0.04(0.02, 0.06) p=0.004), and L1-L4 BA (1.0(0.1, 2.0), p=0.04) and lean mass showed significant increases. There was a decline in the TBLH BA (-57.2(-113.1, -1.3), p=0.05) at 24 months

#### Change from visit 1 to visit 3

The next table compares changes between visit 1 and visit 3. Only 2/10 young people were below their baseline weight.

Table 32 - DXA Data – Change from visit 1 to visit 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **%**  **Change** |
| TBLH BMD  (gm/cm2) | 10 | 1. 16  (0. 08) | 1.19  (0. 08) | 0. 04  (0. 01, 0. 06) | 0. 012\* | 3.4 |
| TBLH BA  (cm2) | 10 | 1980. 8  (244. 6) | 1958. 3  (252. 8) | -22. 5  (-97. 5, 52. 5) | 0. 515 | -1.1 |
| TBLH BMC  (gm) | 10 | 2300. 1  (293. 0) | 2343. 9  (334. 5) | 43. 9  (-20. 6, 108. 4) | 0. 158 | 1.9 |
| L1-L4 BMD  (gm/cm2) | 9 | 1. 24  (0. 15) | 1. 28  (0. 16) | 0. 04  (-0. 02, 0. 10) | 0. 143 | 3.2 |
| L1-L4 BA  (cm2) | 9 | 56. 9  (6. 7) | 58. 8  (7. 1) | 2. 0  (0. 9, 3. 0) | 0. 003\* | 3.5 |
| L1-L4 BMC  (gm) | 9 | 70. 3  (10. 5) | 75. 6  (14. 0) | 5. 3  (1. 0, 9. 5) | 0. 021\* | 7.5 |
| TBLH Fat Mass  (gm) | 9 | 71978  (13764) | 75076  (20039) | 3098  (-10979, 17175) | 0. 625 | 4.3 |
| Truncal Fat Mass | - | - | - | - | - |  |
| TBLH Lean Mass  (gm) | 9 | 58665  (10561) | 61630  (8530) | 2965  (306, 5624) | 0. 033\* | 5.1 |
| TBLH Fat Mass % | 9 | 55. 0  (3. 3) | 54. 3  (7. 7) | -0. 8  (-5. 1, 3. 6) | 0. 697 | -1.5 |
| % Truncal Fat Mass | - | - | - | - | - |  |

With weight regain in 8/10 participants at 24 month follow up, the TBLH BMD increased (0.04(0.01, 0.06), p=0.012) as did L1-L4 BA (2(0.9,3.0), P=0.003) and L1-L4 BMC (5.3(1.0,9.5) p=0.002). Lean Mass increased over the 18 months after balloon removal (2965(306, 5624) p=0.033).

Physical activity questionnaires (self reported) were completed by the young people at baseline, at 6-month post balloon removal, 12, 18 and 24 month follow up. This showed a small reduction at 6 months (mean difference 0.19; p = 0.891), returned to baseline at 12 months (mean difference 0.09, p = 0.992) but decreased again at 24 months.

Cardiorespiratory fitness as identified by the modified Balke protocol peaked at 6 months (mean difference 282.7, p = 0.013\*) with improvements maintained at 12 months. These assessments were carried out by the science and exercise officer and have been published previously(317).

#### Summary

Table 36 outlines the change in TBLH FM %, LM %, TBLH BMD, TBLH BA and BMC, Lumbar area BMD, BA and BMC between baseline, balloon removal at 6 months and 2 years (18 months after balloon removal)

Table 33 - Changes in TBLH FM %, TBLH LM %, TBLH BMD, TBLH BMD Z score, TBLH BA, TBLH BMC, L1-L4 BMD, L1-L4 BMD Z score, L1-L4 BA, L1-L4BMC over the 24-month period

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Before balloon insertion N=12**  **Mean (±SD)** | **After balloon removal (6 months) N=12**  **Mean (±SD)** | **At 2 years – 18 months post balloon removal**  **N=10**  **Mean (±SD)** | **Mean difference between baseline and balloon removal at 6 months**  **P value** | **Mean difference between baseline and balloon removal at 24 months**  **P value** |
| TBLH fat mass  % | 54. 9  (3. 5) | 52. 8  (5. 2) | 54. 9  (7. 5) | -2. 1  (-5. 9,1. 7)  [<0.05] \* | 0. 0  (-5. 0,5. 0)  [0] |
| TBLH lean mass % | 44. 77  (3. 4) | 46. 58  (5. 0) | 44. 92  (7. 6) | 1. 81  (-1. 9,5. 5)  [0. 42] | 0. 15  (-4. 9,5. 2)  [0. 02]\* |
| TBLH BMD  g/cm2 | 1. 15  (0. 07) | 1. 15  (0. 06) | 1. 19  (0. 08) | 0. 002  (-0. 03, 0. 03)  [0. 85] | 0. 04  (0. 01, 0. 06)  [0. 06] |
| TBLH BMD z score | 1. 7  (1) | 1. 64  (0. 9) | 1. 97  (1. 1) | -0. 06  (-0. 9,0. 7)  [0. 3] | 0. 27  (-0. 65,1. 19)  [0. 3] |
| TBLH BA  cm2 | 2010. 2  (240. 7) | 2056. 5  (205. 3) | 1958. 3  (252. 8) | 46. 4  (-15. 8,108. 5)  [0. 13] | -22. 5  (-97. 5, 52. 5)  [0. 09] |
| TBLH BMC  (gm) | 2307. 9  (287. 6) | 2368. 6  (254. 1) | 2343. 9  (334. 5) | 60. 7  (5. 5, 115. 9)  [0. 034]\* | 43. 9  (-20. 6, 108. 4)  [0. 14] |
| L1-L4 BMD(g/cm2) | 1. 23  (0. 2) | 1. 26  (0. 2) | 1. 28  (0. 2) | 0. 03  (0. 01, 0. 04)  [0. 007]\* | 0. 04  (-0. 02, 0. 10)  [0. 27] |
| L1-L4 BMD z score | 0. 9  (1. 2) | 0. 87  (1. 2) | 0. 76  (1. 3) | -0. 03  (-1. 09,1. 03)  [0.6] | -0. 14  (-1. 26,0. 98)  [0. 11] |
| L1-L4 BA(cm2) | 57. 4  (7. 6) | 58. 1  (7. 5) | 58. 8  (7. 1) | 0. 8  (0. 4, 1. 2)  [0. 002]\* | 2. 0  (0. 9, 3. 0)  [0. 27] |
| L1-L4 BMC(gm) | 70. 5  (13. 0) | 73. 0  (13. 3) | 75. 6  (14. 0) | 2. 5  (1. 4, 3. 6)  [0. 001]\* | 5. 3  (1. 0, 9. 5)  [0. 39] |

**Table key:** TBLH = Total body less head BMD = Bone Mineral Density BMC = Bone Mineral Content

BA = Bone Area

#### Discussion

Our study is the first prospective longitudinal study looking at the impact of weight loss due to intragastric balloon insertion accompanied by a lifestyle programme in a group of severely obese adolescents. There is not much literature on children in this area. Adolescence is a time of intense bone mass accrual, and bone formation to reach peak bone mass. Failure to do this results in a long-term increased risk of osteoporosis. There are numerous adult studies showing loss of bone mass and density after bariatric surgery with a correlation between the degree of weight and bone loss(285, 318). Thus, one of our aims was to demonstrate whether weight loss due to the balloon has a significant impact on bone mass accrual over time.

As expected, the obese young people in our study had a higher starting point for their TBLH BMD Z score (mean(SDs) of 1.7 (1.0)) as seen in a previous study looking at adolescents undergoing bariatric surgery (225). The hybrid study from the TEEN LABS consortium was the first to report (2011) longitudinal bone changes in a group of 61 adolescents following gastric bypass. Their mean age was 17.3 years (older, 51 female) and they were heavier (mean BMI of 54.4 ±6.8, WB BMD Z score at baseline 1.5 versus BMI 46.4±5.6, TBLH BMD Z score 1.7) than our cohort). These young people experienced a mean weight loss of 44 kg compared to 7 kg in our study. Their BMC decreased by 7.4 percent while WB BMD z score continued to decrease at 1 and then 2 years but remained above baseline (0.1). This would be significant if the decline continued with weight loss. Though the bone loss was significantly associated with the amount of weight loss, only 14 percent of this could be explained by the change in weight suggesting that other factors such as decreased food intake, malabsorption of vitamins and minerals, reduced mechanical loading and other mediators such as adipokines and incretins may play a role.

In contrast to the Kaulfer study, the BMD z score of our participants only reduced to 1.64 from 1.7 (non-significant change) after weight loss and was still well above baseline. This of course is with a modest weight loss of 5 percent (7 kg, BMI Change -2.5 kg/m2), however the weight loss was clinically significant and is quoted as the amount needed to bring about clinically significant improvement in co-morbidities. The Kaulfer study used WB DXA on a Hologic densitometer; the generation of Z scores is different dependend on the DXA manufacturer and the paediatric normative data bate used. We used a lunar iDXA and calculated TBLH and lumbar parameters as per recommendations for young people.

For our cohort, at the 2-year mark, when weight regain had been seen in 8/10 individuals, the TBLH BMD z score was well above baseline (1.97(1.1)) and there had been a significant gain in TBLH BMD (0.04 gm/cm2(0.01,0.06), p=0.012).

The weight loss seen in our study was modest when compared to bariatric surgery but higher than that seen in some behavioral intervention programmes. The study by the Kelley group of 91 obese adolescents reported a BMI reduction of 0.4 kg/m2 in the lifestyle intervention group at 12 months with the main impact seen at 6 months followed by a plateau effect or increases in weight at the 12 month follow up visit which is not unusual when the intensity of the intervention wanes. They looked at fat mass index (obtained by dividing the fat weight in kilograms with height in metres squared rather than using total weight as done for BMI), lean mass index, visceral and subcutaneous fat as well as bone mineral content (assessed by DXA) over the 12-month period. This group of young people were younger and weighed less than our cohort (12.2 years versus 15.3 years, BMI 33.0 versus 46.4 kg/m2). Differences were seen in the fat mass index (0.46 in standard care versus -0.77 in the intervention group) as well as in the subcutaneous fat area, but no other differences were noted in the body composition due to the modest weight loss. Mean BMI change was reported separately for boys and girls (-0.5 kg/m2(-1.3,0.2) and 0.7kg/m2(0.2,1.1) respectively compared to -2.5 kg/m2 (-7.2, 2.2) in our cohort(319). We did not analyse males and females separately due to the small numbers.

In our cohort, the total BMC increased from 2308 (287.6) to 2368 gms (254.1) (approx. 2.5 percent increase) in the initial 6 months when weight loss was experienced. The correlation between weight loss and change in BMC and BMD Z score was not significant.

We have shown a significant reduction in truncal fat mass over a 6-month period but this was accompanied by improvements in bone mineral density suggesting that despite weight loss, bone mass accrual continued.

In another study looking at non-surgical weight loss in 92 obese female adolescents (Tanner stage 2 to 4) who took part in a 6-month weight loss intervention, mean weight at 12 months increased like in our group who were followed up till 24 months. There was a correlation between changes in body weight and changes in bone measurement (TBLH and lumbar spine BMD/BMC) but those who lost weight did not show a reduction in bone mineral content or density, though their rate of growth had declined compared to rest of the study subjects whose bone growth rate was similar to their normal weight peers(320). All but one of the young people in our cohort were Tanner stage 5 and there was no change in height sds over the 2 years as the majority had completed their growth.

Lumbar region z score was above average in our study at baseline (0.9) and showed a non-significant decrease over the 6 and 24 months but remained above baseline (0.87, 0.76). The absolute values for L1-L4 BMD, BMC and BA all increased significantly despite the weight loss at 6 months. There was a significant negative correlation between change in truncal fat mass and L1-L4 BMD (r=-0.77, p=0.009) and BMC (r=-0.77, p=0.008). This is important as previous studies have shown that it is the reduction in truncal fat mass that impacts negatively on bone mass and bone mineral density. Reliability of the data in severe obesity is a factor as well as truncal fat mass loss would impact on the lumbar spine data as well.

Most importantly, despite modest weight loss, lumbar spine bone mass accrual continued. This is important as lumbar spine bone mass accrual will continue beyond TB(194).

Skeletal consequences after bariatric procedures are usually dependent on the amount of weight loss seen and the type of procedure (whether restrictive, malabsorptive or both). In some adult studies, no changes or a slight increase in lumbar spine BMD has been seen after gastric banding (restrictive procedure like the balloon). Von-Mach showed significant reduction in lumbar BMC (2968 gms to 2621 gms, p=0.005) in the bypass group (BMI reduction of 12.2 kg/m2, p=0.006) alongside an increase in markers of bone turnover(both formation and resorption with serum osteocalcim and urinary deoxypyridinoline) (19 patients, 9 band, 4 bypass and 6 controls), with no change in the lumbar BMC in the band group though BMI change was significant (-7kg/m2(p=0.0010) (321) .

The sleeve gastrectomy which is both restrictive and malabsorptive, both reductions and increase in Lumbar Spine BMD have been reported. The study which showed a 5.7% increase at one year and 7.9 % at 2 years had 42 participants (39 female, mean BMI of 51.2 kg/m2, mean excess BMI loss of approximately 80%) was however retrospective in design, and there was a potential bias in those who underwent DXA(322), therefore may be less reliable. Changes were not correlated with weight loss but showed a positive correlation with Vitamin D levels and an inverse one with PTH.

Pre -surgical vitamin and mineral deficiencies also play a role in changes seen post-surgery. A study looking at the impact of dietary calcium and vitamin D after bariatric surgery did not show any difference in bone mass with supplementation with 1.2 gms of calcium and 8 mcg of vitamin D in those in the pre-menopausal RYGB group with low bone mass compared to the control group three years after the RYGB procedure. The bone turnover markers were higher in the RYGB group and again did not change after supplementation. So, it maybe that higher amount of supplementation is required to bring about a change. In the post-menopausal group, the Lumbar Spine BMD and BMC was higher than controls though femoral neck BMC was lower post-surgery (323).

Some prospective studies have shown a steady decline with decreases in bone mineral density at hip (7.8 %), trochanter (9.3%) and total body (1.6%) accompanied by significant decreases in bone mineral content within 3-9 months after RYGB (25 obese patients matched with 30 controls with 15 followed up prospectively after surgery who had an 8% fall in BMI) (324).

However, in another study, the reduction seen at the total hip and femoral neck following RYGB in 30 morbidly obese adults was not then corroborated in vBMD measurements using QCT. (325)

Most studies (including ours) report high rates of Vitamin D deficiency pre-operatively (up to 95 percent vitamin D deficient subjects in some), however though supplementation (variable dosing) is advised this can rarely be confirmed and therefore the impact of this on bone health cannot be quantified.

Vitamin D levels between 23-26 ng/ ml were seen in one study of 23 obese adults (mean BMI 47 kg/m2) both before and after the procedure though there had been almost a tripling of the amount of Vitamin D supplements suggesting significant malabsorption (285). In this study, patients lost a mean of 45 kilos at 1 year. Lumbar spine and distal radius measurements did not show any change in this study but total BMD, Hip and femoral neck density declined and the hip BMD decline correlated with the amount of weight lost. In our study, supplementation was encouraged with a multivitamin capsule providing 400-1000 IU of Vitamin D but there was no significant change in Vitamin D levels from baseline.

Lean mass increased in our cohort at balloon removal despite clinically significant weight loss at 6 months. Lean mass continued to increase with the weight gain seen at 24 months (0.15%(-4.9,5.2) p=0.02). This is in contrast to a previous study looking at the effects of a multidisciplinary programme (moderate energy restriction accompanied by endurance and weight training) to help severely obese adolescents (26, aged 12-16 with mean BMI of 33.9 kg/m2) lose weight, which resulted in a loss of both total body weight and free fat mass (FFM) and though fitness improved, energy expenditure declined even after correcting for the FFM(326).

This is important as the aim is to try and maintain the lean mass due to its role in metabolic rate regulation. Unfortunately, we did not measure energy expenditure at rest before and after the intragastric balloon placement. The changes seen in the Health-Related Quality of Life (Qol), Physical activity and Cardiorespiratory fitness have been reported by researchers from Sheffield Hallam University (317). The physical activity was self-reported using the physical activity questionnaire for adolescents (PAQ-A|) with a focus on spare time physical activity, lunch time physical activity, weekend and evening activity etc. The participants scaled themselves from 1-5 (from not active to very active). This showed an initial decline at 6 months (mean difference 0.19, p=0.89), which returned to baseline (mean difference 0.09, p=0.9) at 12 month follow up but declined again at 24 months. Cardiorespiratory fitness, an objective measure compared to the subjective physical assessment score improved at 6 months (mean difference 282.7, p=0.013) and persisted above baseline at 12 months which could suggest that the young people may have underestimated their physical activity and this may have a role in the increase seen in lean mass. Obese young people with higher cardiorespiratory fitness have lower levels of body adiposity(327); we saw a significant decrease in both the truncal fat mass and waist circumference over the 6 months following the intragastric balloon procedure.

Weight loss usually results in loss of both fat and lean mass and the loss of lean mass per se can also play a role in bone loss due to a potential increase in falls and fracture risk.

A study evaluating bone mineral density in 59 morbidly obese women three years after surgery showed that the BMD loss at the femoral neck had a positive correlation with the percentage of lean mass loss (p=0.045). (328).

Thus, the increased lean mass may have played a protective role in our cohort.

Currently, many of the guidelines for monitoring patients undergoing bariatric surgery recommend pre-operative and annual DXA scanning until a steady threshold is reached for the malabsorptive plus restrictive procedures (RYGB, BPD and BPD/DS). It is not clear what approach should be adopted for purely restrictive procedures such as the band and the balloon. In case of young people who are still accruing bone mass, this monitoring is even more crucial, however there are several limitations regarding the interpretation of the data.

#### 8.1.6 Limitations:

One of the limitations of the study is that we have used age related z-score as opposed to body-size as size-related artefactual increase in aBMD with increasing height and weight is well recognised. However, this was discussed with my supervisors and as we are dealing with individuals so far from the average size, it wasn’t clear that any of the multiple suggested adjustment processes would be applicable.

While DXA scanning in our study did not highlight any significant reduction following weight loss, and all attempts were made to accommodate the fact that the participants were severely obese, we know that fat mass and obesity per se can affect accuracy. Therefore, the reliability of the data in this cohort will always be questionable.

In a study looking at a spine phantoms for DXA and QCT in 13 adults, wherein up to 12 kg of fat layering was added in and then measurements made at lumbar spine and proximal femur, the impact on the DXA was significant with more variability in measurements recorded but not on the QCT. (329) . This was due to the X-ray attenuation due to the high degree of soft tissue in scan areas.

When 3 groups of women (normal, overweight and obese, total n=102) underwent duplicate DXA scans after repositioning, the percentage coefficient of variation was significantly higher at all 3 areas (lumbar spine, hip and total body) in the obese group suggesting caution is warranted particularly in this group of people. (330).

When the soft tissue depth is >25 cm, then the impact on bone mineral density is significant as shown in study where a substantial decline in BMD was noted following a weight loss programme, but there was no associated change in bone mineral content suggesting the decline in BMD noted may not be reliable.(318) (14 women in a 15 week weight loss programme who lost a mean of 15.6 kg weight)

The scans were done by the same 3 trained senior radiographers and positioning was carefully documented though this would not obviate the inherent errors described above.

It is reassuring that age appropriate increases were seen in both TBLH BMD and lumbar spine BMD z scores despite clinically significant weight loss in our cohort.

In summary, the modest but clinically significant weight loss seen at 6 months secondary to intragastric balloon insertion did not seem to have a detrimental effect on lumbar spine and TBLH BMD change in this cohort of severely obese young people.

### HRpQCT

Obese young people are more prone to fracture compared to their normal weight peers. This could be related to several factors such as a higher likelihood of falls, and the falls themselves may be associated with a greater force which would also be significant. Other factors include sedentary lifestyle, unhealthy diets as well as the impact of of excessive adipose tissue on the development of the skeleton(331). By intervening with weight loss bariatric interventions, which are known to be associated with decreased bone mass and increased fracture risk, we maybe putting these young people at more risk of fractures.

Therefore, alongside DXA, HRpQCT was planned in our study to longitudinally study bone microarchitecture and bone strength following intragastric balloon placement with follow up at 2 years.

All 12 participants had baseline HRpQCT data for both radius and tibia.

11 had 6-month data for radius (excluding BOB05 who did not attend)

10 had 6-month data for tibia (excluding BOB05 who did not attend and BOB12 who started to feel unwell and complained of cramps and left after the radius scan).

24-month data was obtained for 7/12 at the tibia (BOB06 and BOB07 had poor quality images, BOB11 was unable to fit her leg into the cast (size issues), BOB09 did not attend and BOB12 had withdrawn from the study).

24-month data was obtained for 7/12 at the radius (BOBO6, BOB07, BOB10 had poor quality images, BOB09 did not attend and BOB12 had withdrawn from the study).

#### Change in Weight, Height and BMI over 2 years

There was a significant reduction in weight SDS and BMI SDS at the 6-month visit but no difference was noted at 24 months (see tables 34, 35, 36).

Table 34 - Height, weight and BMI SDS change from visit 1 to visit 2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 2**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** |
| Height SDS | 11 | 1. 05 (1. 17) | 1. 09 (1. 25) | 0. 04 (-0. 12, 0. 20) | 0. 588 |
| Weight SDS | 11 | 5.19 (0. 64) | 4. 81 (0. 72) | -0. 38 (-0. 62, -0. 15) | 0. 005\* |
| BMI SDS | 11 | 3. 98 (0. 37) | 3. 71 (0. 33) | -0. 27 (-0. 43, -0. 10) | 0. 005\* |

Table 35 - Height, weight and BMI SDS change from visit 2 to visit 3

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 2**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** |
| Height SDS | 9 | 1. 06 (1. 33) | 1. 24 (1. 46) | 0. 18 (0. 04, 0. 31) | 0. 017 |
| Weight SDS | 9 | 4. 51 (0. 68) | 4. 89 (0. 81) | 0. 38 (-0. 12, 0. 88) | 0. 119 |
| BMI SDS | 9 | 3. 79 (0. 31) | 4. 05 (0. 71) | 0. 27 (-0. 24, 0. 77) | 0. 257 |

Table 36 - Height, weight and BMI SDS change from visit 1 to visit 3

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** |
| Height SDS | 10 | 1. 01 (1. 10) | 1. 13 (1. 42) | 0. 12 (-0. 18, 0. 41) | 0. 394 |
| Weight SDS | 10 | 4. 92 (0. 71) | 4. 91 (0. 77) | -0. 01 (-0. 51, 0. 48) | 0. 954 |
| BMI SDS | 10 | 4. 05 (0. 35) | 4. 08 (0. 68) | 0. 03 (-0. 52, 0. 59) | 0. 896 |

#### Using Normative data

Centile charts with normative sex, ethnicity, age specific data for both Asian and Caucasian adolescents have only recently been published (247). The young people in our study were above the 97th centile for the ultimate fracture load on the finite element analysis at both the distal tibia and radius at baseline, 6 months (balloon removal when weight sds decreased by 0.38, p=0.005)) and 24 months.

All the young people had a tibial BMD and radial BMD within normal range.

The results for BOB09 were consistently different across the board (lower cortical area, cortical thickness, cortical tissue mineral density and high periosteal and endosteal diameter).  On the scans, there appeared to be very little cortical bone but the bone was large. There was no history of previous fractures. This was discussed with Professor Bishop who explained that cortical expansion resulting in increased bone width could be an adaptive whole bone change in other settings where bone was weak and may imply an underlying problem that was worth further investigation. Plain spine films were done in the first instance to look for vertebral deformity. There appeared to be a generalised reduction in vertebral body height in the lower thoracic and upper lumbar spine but no anterior wedging suggesting fracture. The age matched z-score = 0.2. He was reviewed and discharged. This difference could be because he had not completed puberty where all the other were Tanner 5. If so it would have implications for using balloons in those who have not completed puberty. It could of course (as n=1) just be coincidence. Further work is needed to clarify this.

#### Visit 1-2

HR-pQCT densitometric measurements included total density (Dtot, milligrams per cubic centimeter), trabecular density (Dtrab, milligrams per cubic centimeter), and cortical density (Dcort, milligrams per cubic centimeter). Measures of microstructural properties included trabecular number (Tb.N, 1/millimeters), trabecular thickness (Tb.Th, millimeters), trabecular separation (Tb.Sp, millimeters), bone volume fraction (BV/TV, percent), and cortical thickness (Ct.Th, millimeters).

FEA-derived variables used in our analyses included the following: stiffness (kiloNewtons/mm), estimated failure load (kilonewtons), the percentage of load carried by the trabecular bone at the distal and proximal surface of the volume of interest (% load trab distal and % load trab proximal, respectively. The estimated failure load is a calculation of the applied load that results in > than a 2 percent change in the strain value of 3500.

Change in radial and tibial HRpQCT parameters between visit 1 &2 is depicted in

Table 37 below. Significant changes (p<0. 05 are marked as an asterisk).

Table 37 - Radial and Tibial HRpQCT parameters – Change from visit 1 to visit 2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tibia** | | | | | | |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 2**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **% change** |
| Total Area (T. Ar in mm2) | 10 | 900. 9 (241. 3) | 894. 4 (233. 0) | -6. 5 (-14. 6, 1. 6) | 0. 104 | -0. 7 |
| Cortical Area (Ct. Ar in mm2) | 10 | 122. 7 (38. 0) | 125. 1 (39. 6) | 2. 4 (0. 1, 4. 7) | 0. 044\* | 1. 95 |
| Trabecular Area (Tb. Ar, in mm2) | 10 | 771. 7 (260. 3) | 769. 5 (260. 5) | -2. 2 (-4. 9, 0. 5) | 0. 094 | -0. 3 |
| Total BMD (D100 in mg/ccm) | 10 | 310. 4 (54. 4) | 314. 0 (55. 8) | 3. 7 (-0. 6, 7. 9) | 0. 084 | 1. 2 |
| Cortical BMD (Ct. BMD in mg/ccm) | 10 | 843. 1 (100. 0) | 854. 1 (100. 4) | 11. 0 (4. 1, 17. 9) | 0. 006\* | 1. 3 |
| Trabecular BMD (Tb. BMD in mg/ccm) | 10 | 205. 4 (18. 0) | 205. 5 (18. 5) | 0. 1 (-3. 3, 3. 4) | 0. 958 | 0. 05 |
| Cortical thickness (Ct. Th in mm) | 10 | 1. 10 (0. 42) | 1. 12 (0. 42) | 0. 02 (0. 002, 0. 040) | 0. 035\* | 1. 8 |
| Trabecular BV/TV (Tb. BV/TV) | 10 | 0. 171 (0. 015) | 0. 171 (0. 015) | 0. 0001 (-0. 003, 0. 003) | 0. 937 | 0. 05 |
| Trabecular number (Tb. N, 1/mm) | 10 | 2. 55 (0. 42) | 2. 56 (0. 35) | 0. 01 (-0. 11, 0. 13) | 0. 858 | 0. 4 |
| Trabecular thickness (Tb. Th, in mm) | 10 | 0. 069 (0. 013) | 0. 068 (0. 012) | -0. 001 (-0. 003, 0. 002) | 0. 591 | -1. 5 |
| Trabecular separation (Tb. Sp in mm) | 10 | 0. 333 (0. 060) | 0. 330 (0. 053) | -0. 003 (-0. 019, 0. 013) | 0. 658 | -0. 9 |
| Cortical Porosity (Ct. Po) | 10 | 0. 050 (0. 028) | 0. 045 (0. 020) | -0. 005 (-0. 011, 0. 001) | 0. 095 | -10 |
| Mean cortical pore diameter (Ct. Po. Dm) | 10 | 0. 152 (0. 016) | 0. 154 (0. 013) | 0. 002 (-0. 003, 0. 008) | 0. 358 | 1. 3 |
| S | 10 | 256. 8 (27. 5) | 260. 7 (29. 8) | 3. 8 (-2. 3, 10. 0) | 0. 193 | 1. 4 |
| F. ult | 10 | 13. 3 (1. 5) | 13. 4 (1. 6) | 0. 2 (-0. 1, 0. 4) | 0. 106 | 1. 5 |
| (Tb. F/TF)dist | 10 | 60. 9 (12. 9) | 60. 6 (12. 4) | -0. 3 (-1. 0, 0. 4) | 0. 393 | -0. 5 |
| (Tb. F/TF)prox | 10 | 43. 6 (13. 1) | 43. 7 (13. 4) | 0. 1 (-1. 0, 1. 1) | 0. 848 | 0. 2 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Radius** | | | | | | |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 2**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **% change** |
| Total Area (T. Ar in mm2) | 11 | 303. 0 (60. 3) | 297. 0 (58. 6) | -6. 1 (-8. 9, -3. 2) | 0. 001\* | -2 |
| Cortical Area (Ct. Ar in mm2) | 11 | 52. 1 (13. 2) | 54. 6 (9. 6) | 2. 5 (-3. 1, 8. 0) | 0. 343 | 4. 8 |
| Trabecular Area (Tb. Ar, in mm2) | 11 | 245. 1 (65. 5) | 242. 4 (64. 8) | -2. 7 (-7. 2, 1. 9) | 0. 221 | -1. 1 |
| Total BMD (D100 in mg/ccm) | 11 | 312. 4 (47. 1) | 322. 8 (43. 5) | 10. 3 (-0. 3, 21. 0) | 0. 055\* | 3. 3 |
| Cortical BMD (Ct. BMD in mg/ccm) | 11 | 792. 7 (74. 3) | 806. 7 (72. 8) | 14. 0 (8. 3, 19. 6) | <0. 001\* | 1. 8 |
| Trabecular BMD (Tb. BMD in mg/ccm) | 11 | 186. 2 (19. 8) | 190. 3 (21. 1) | 4. 1 (0. 5, 7. 6) | 0. 028\* | 2. 2 |
| Cortical thickness (Ct. Th in mm) | 11 | 0. 74 (0. 24) | 0. 77 (0. 19) | 0. 03 (-0. 06, 0. 11) | 0. 479 | 4 |
| Trabecular BV/TV (Tb. BV/TV) | 11 | 0. 155 (0. 017) | 0. 158 (0. 018) | 0. 003 (0. 001, 0. 006) | 0. 025\* | 1. 9 |
| Trabecular number (Tb. N, 1/mm) | 11 | 2. 27 (0. 18) | 2. 28 (0. 21) | 0. 004 (-0. 11, 0. 11) | 0. 942 | 0. 2 |
| Trabecular thickness (Tb. Th, in mm) | 11 | 0. 068 (0. 006) | 0. 070 (0. 009) | 0. 002 (-0. 002, 0. 006) | 0. 349 | 2. 9 |
| Trabecular separation (Tb. Sp in mm) | 11 | 0. 374 (0. 033) | 0. 372 (0. 036) | -0. 002 (-0. 018, 0. 015) | 0. 842 | 0. 5 |
| Cortical Porosity (Ct. Po) | 11 | 0. 028 (0. 018) | 0. 035 (0. 037) | 0. 007 (-0. 010, 0. 238) | 0. 391 | 25 |
| Mean cortical pore diameter (Ct. Po. Dm) | 11 | 0. 141 (0. 008) | 0. 146 (0. 014) | 0. 005 (-0. 001, 0. 011) | 0. 111 | 3. 5 |
| S | 11 | 89. 0 (9. 6) | 91. 1 (7. 6) | 2. 1 (-4. 1, 8. 4) | 0. 468 | 2. 4 |
| F. ult | 11 | 4. 6 (0. 5) | 4. 7 (0. 5) | 0. 1 (-0. 2, 0. 4) | 0. 488 | 2. 2 |
| (Tb. F/TF)dist | 11 | 53. 2 (9. 2) | 55. 1 (9. 9) | 2. 0 (-2. 1, 6. 0) | 0. 309 | 3. 8 |
| (Tb. F/TF)prox | 11 | 26. 1 (8. 1) | 28. 0 (9. 9) | 1. 9 (-1. 5, 5. 4) | 0. 241 | 7. 2 |

**Summary of findings visit 1-2:**

**Tibia**

Tibial Cortical Area (2.4 mm2 (0.1,4.7), p=0.04), Tibial Cortical BMD (11 gm/ccm (4.1,17.9), p=0.006), Tibial Cortical Thickness (0.02mm (0.002,0.04), p=0.035) all increased over the 6months when significant change in weight SDS (-0.38, p=0.005) was experienced. Cortical porosity showed a reduction of 10 percent at the tibia which was not significant.

**Radius**

At the Radius, Total BMD, (10.3 mg/ccm (0.3,21), p=0.05), cortical BMD (14 mg/ccm (8.3, 19.6), p<0.001), trabecular BMD (4.1 mg/ccm (0.5,7.6), p=0.028), trabecular BV/TV all increased (0.003 (0.001,0.006), p=0.025).

There was no significant change in any of the other parameters.

Total area decreased significantly over the 6 months at the radius (-6.1(-8.9,3.2), p=0.001).

Cortical porosity showed a 25 percent increase at the radius; this was not accompanied by changes in mean cortical pore diameter.

There were no significant changes in the strength parameters between visit 1 and 2 when significant change in weight and BMI SDS was seen.

Figure 35 and 36 show the changes in mean bone microarchitecture and strength between visit 1 and 2 when significant change in weight and BMI SDS was seen.

Figure 35 - Change in tibia and radius HRpQCT between visit 1 and 2 (Circles represent the mean and lines represent the 95% confidence intervals)

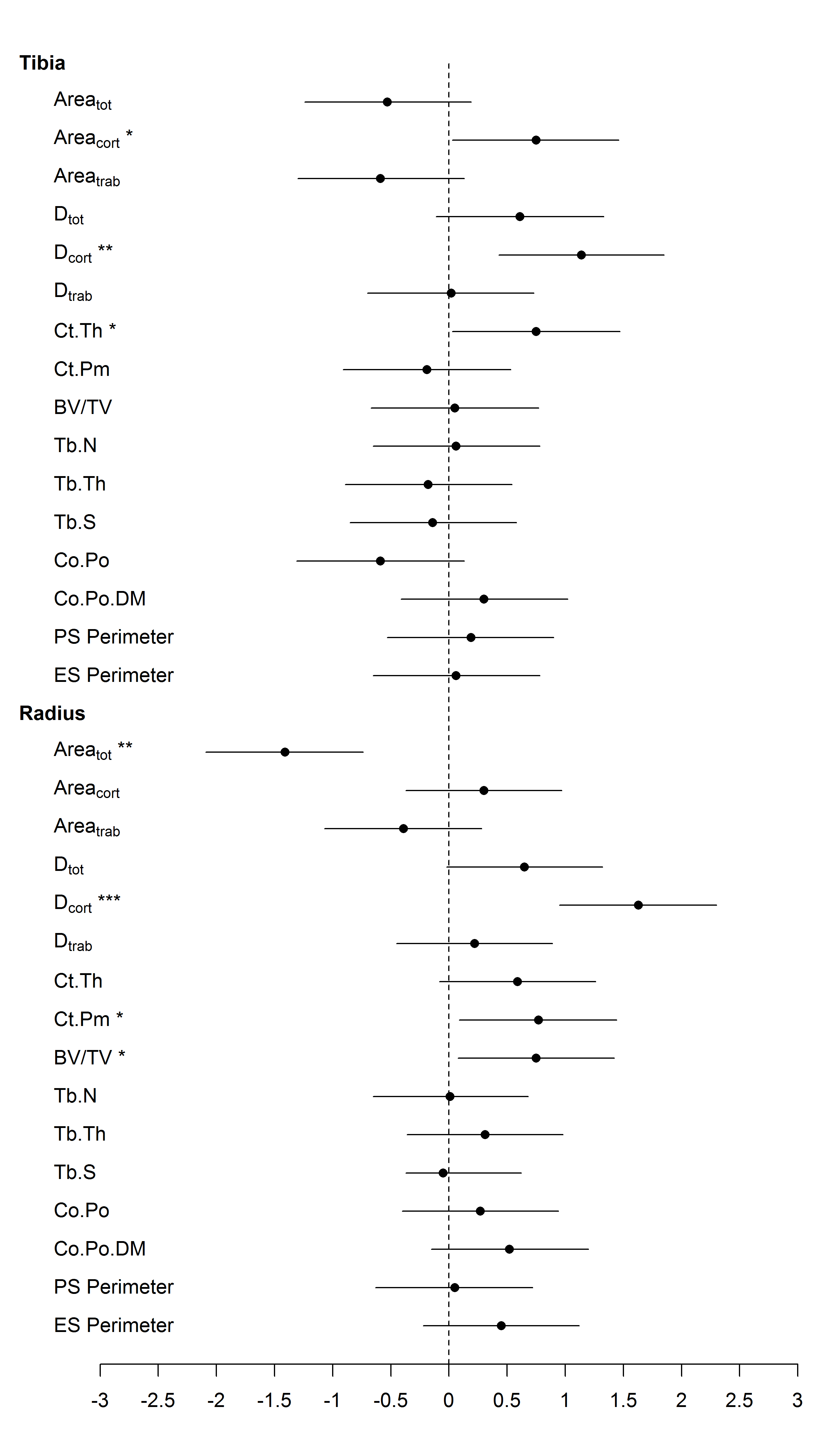
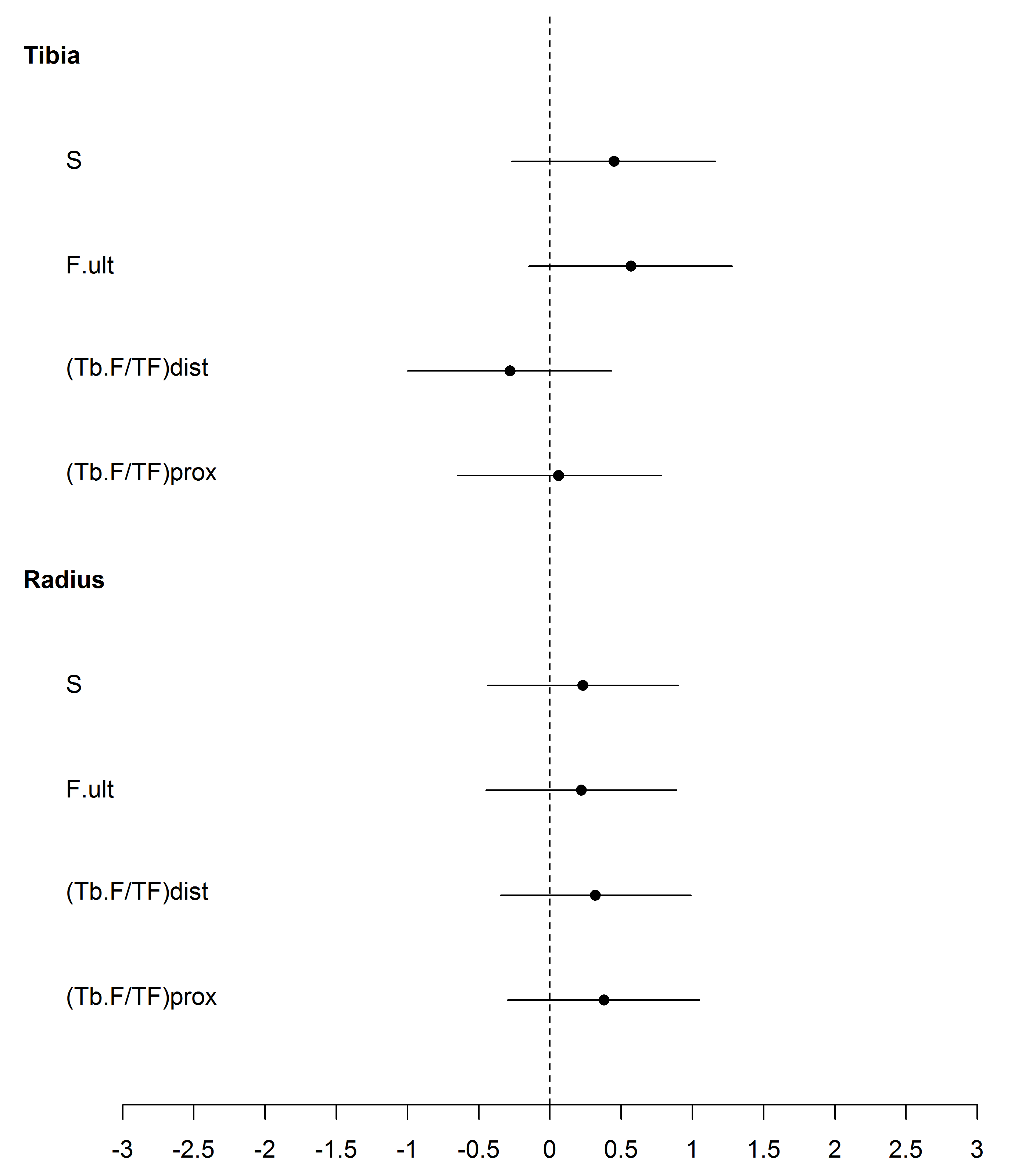


Figure 36 - Change in bone strength markers between visit 1 and 2 the radius and tibia



#### Visit 2-3

Table 38 - Radial and Tibial HRpQCT parameters – Change from visit 2 to visit 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tibia** | | | | | | |
|  | **N** | **Visit 2**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **% change** |
| Total Area (T. Ar in mm2) | 6 | 895. 2 (189. 5) | 898. 0 (192. 7) | 2. 8 (-2. 8, 8. 4) | 0. 256 | 0. 3 |
| Cortical Area (Ct. Ar in mm2) | 7 | 134. 4 (32. 2) | 138. 8 (30. 6) | 4. 4 (1. 9, 6. 8) | 0. 005\* | 3. 3 |
| Trabecular Area (Tb. Ar, in mm2) | 7 | 729. 7 (206. 8) | 726. 7 (206. 8) | -3. 0 (-4. 9, -1. 1) | 0. 009\* | -0. 4 |
| Total BMD (D100 in mg/ccm) | 7 | 323. 2 (57. 9) | 325. 4 (56. 1) | 2. 2 (-1. 5, 5. 9) | 0. 201 | 0. 6 |
| Cortical BMD (Ct. BMD in mg/ccm) | 7 | 879. 0 (57. 9) | 888. 7 (44. 8) | 9. 7 (-3. 8, 23. 1) | 0. 130 | 1. 1 |
| Trabecular BMD (Tb. BMD in mg/ccm) | - | - | - | - | - |  |
| Cortical thickness (Ct. Th in mm) | 7 | 1. 21 (0. 37) | 1. 24 (0. 36) | 0. 03 (0. 010, 0. 055) | 0. 012\* | 2. 4 |
| Trabecular BV/TV (Tb. BV/TV) | 7 | 0. 173 (0. 017) | 0. 171 (0. 017) | -0. 002 (-0. 004, 0. 0003) | 0. 080 | -1. 2 |
| Trabecular number (Tb. N, 1/mm) | 7 | 2. 49 (0. 39) | 2. 46 (0. 35) | -0. 03 (-0. 14, 0. 08) | 0. 587 | -1. 2 |
| Trabecular thickness (Tb. Th, in mm) | 7 | 0. 071 (0. 013) | 0. 071 (0. 012) | -0. 003 (-0. 003, 0. 003) | 0. 812 | -4. 2 |
| Trabecular separation (Tb. Sp in mm) | 7 | 0. 340 (0. 059) | 0. 343 (0. 055) | 0. 004 (-0. 013, 0. 020) | 0. 605 | 1. 1 |
| Cortical Porosity (Ct. Po) | 7 | 0. 041 (0. 021) | 0. 038 (0. 014) | -0. 004 (-0. 013, 0. 006) | 0. 369 | -10 |
| Mean cortical pore diameter (Ct. Po. Dm) | 7 | 0. 156 (0. 015) | 0. 157 (0. 013) | 0. 001 (-0. 012, 0. 014) | 0. 850 | 0. 6 |
| S | 7 | 264. 3 (26. 9) | 269. 4 (25. 8) | 5. 0 (0. 03, 10. 02) | 0. 049\* | 1. 9 |
| F. ult | 7 | 13. 5 (1. 3) | 13. 8 (1. 3) | 0. 2 (0. 1, 0. 4) | 0. 020\* | 1. 5 |
| (Tb. F/TF)dist | 7 | 59. 4 (9. 0) | 59. 9 (7. 9) | 0. 4 (-0. 8, 1. 7) | 0. 423 | 0. 6 |
| (Tb. F/TF)prox | 7 | 11.941. 9 ( | 40. 8 (9. 4) | -1. 1-1-1. 7, -0. 4) | 0. 008\* | -2. 6 |
| **Radius** | | | | | | |
|  | **N** | **Visit 2**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** |  |
| Total Area (T. Ar in mm2) | 6 | 312. 9 (77. 1) | 328. 8 (88. 9) | 16. 0 (-20. 3, 52. 2) | 0. 310 | 5. 1 |
| Cortical Area (Ct. Ar in mm2) | 6 | 53. 5 (12. 0) | 58. 8 (16. 0) | 5. 3 (-7. 8, 18. 3) | 0. 348 | 9. 9 |
| Trabecular Area (Tb. Ar, in mm2) | 6 | 259. 3 (85. 5) | 268. 6 (99. 7) | 9. 3 (-31. 4, 49. 9) | 0. 583 | 3. 5 |
| Total BMD (D100 in mg/ccm) | 6 | 315. 1 (51. 8) | 326. 8 (59. 9) | 11. 8 (-20. 7, 44. 2) | 0. 395 | 3. 7 |
| Cortical BMD (Ct. BMD in mg/ccm) | 6 | 808. 2 (61. 5) | 824. 5 (66. 0) | 16. 3 (-22. 6, 55. 3) | 0. 330 | 2. 0 |
| Trabecular BMD (Tb. BMD in mg/ccm) | 6 | 185. 3 (15. 8) | 185. 0 (20. 2) | -0. 3 (-6. 7, 6. 1) | 0. 919 | -0. 1 |
| Cortical thickness (Ct. Th in mm) | 6 | 0. 73 (0. 23) | 0. 79 (0. 31) | 0. 07 (-0. 15, 0. 28) | 0. 475 | 9. 5 |
| Trabecular BV/TV (Tb. BV/TV) | 6 | 0. 154 (0. 013) | 0. 154 (0. 017) | -0. 0003 (-0. 005, 0. 005) | 0. 871 | -0. 1 |
| Trabecular number (Tb. N, 1/mm) | 6 | 2. 40 (0. 17) | 2. 41 (0. 19) | 0. 02 (-0. 07, 0. 11) | 0. 631 | 0. 8 |
| Trabecular thickness (Tb. Th, in mm) | 6 | 0. 064 (0. 003) | 0. 064 (0. 005) | -0. 001 (-0. 004, 0. 003) | 0. 618 | 1. 5 |
| Trabecular separation (Tb. Sp in mm) | 6 | 0. 355 (0. 030) | 0. 353 (0. 035) | -0. 002 (-0. 018, 0. 014) | 0. 756 | -0. 5 |
| Cortical Porosity (Ct. Po) | 6 | 0. 028 (0. 017) | 0. 021 (0. 010) | -0. 007 (-0. 015, 0. 001) | 0. 072 | -25 |
| Mean cortical pore diameter (Ct. Po. Dm) | 6 | 0. 141 (0. 009) | 0. 138 (0. 008) | -0. 003 (-0. 010, 0. 005) | 0. 399 | 2. 1 |
| S | 6 | 90. 2 (9. 4) | 94. 3 (10. 8) | 4. 1 (-3. 8, 12. 0) | 0. 240 | 4. 5 |
| F. ult | 6 | 4. 6 (0. 6) | 4. 8 (0. 6) | 0. 2 (-0. 2, 0. 6) | 0. 274 | 4. 3 |
| (Tb. F/TF)dist | 4 | 49. 6 (10. 4) | 48. 9 (14. 5) | -0. 7 (-11. 5, 10. 1) | 0. 856 | 1. 4 |
| (Tb. F/TF)prox | 6 | 28. 6(13. 7) | 27. 0(12. 0) | -1. 5(-7. 5,4. 4) | 0. 535 | -5. 2 |

**From visit 2 to visit 3**, weight gain was seen in the cohort over all, though 2/10 young people continued to lose weight.

**Tibia**

Tibial cortical area (4.4(1.9,6.8), p=0.005) and cortical thickness (0.03(0.01,0.05), p=0.012) increased significantly but tibial trabecular area decreased (3.0, (-4.9, -1.1), p=0.009)

Cortical porosity decreased by 1o % between visit 2 and 3 at the tibia.

**Radius**

There were no significant changes in any of the parameters at the radius.

Cortical porosity decreased by 2o % between visit 2 and 3 at the radius.

Cortical area and cortical thickness showed a 9. 9 and 9. 5 percent increase at the radius though this not significant.

From visit 2-3, ultimate failure load (0.2(0.1,0.4), p=0.05) and stiffness (5(0.03,10,02) p=0.02) increased significantly at the tibia.

However, the percentage load carried proximally by the trabecular bone decreased significantly (p=0.008).

#### Visit 1-3

Table 39 - Radial and Tibial HRpQCT parameters – Change from visit 1 to visit 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tibia** | | | | | | |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **%**  **change** |
| Total Area (T. Ar in mm2) | 7 | 863. 0 (198. 5) | 863. 0 (198. 8) | 0. 1 (-6. 7, 6. 9) | 0. 976 | 0. 01 |
| Cortical Area (Ct. Ar in mm2) | 8 | 132. 5 (28. 8) | 142. 6 (30. 3) | 10. 1 (1. 7, 18. 5) | 0. 024\* | 7. 6 |
| Trabecular Area (Tb. Ar, in mm2) | 8 | 704. 4 (206. 2) | 696. 4 (209. 8) | -8. 0 (-16. 4, 0. 3) | 0. 057 | -1. 3 |
| Total BMD (D100 in mg/ccm) | 8 | 323. 1 (56. 4) | 335. 0 (58. 6) | 11. 9 (1. 6, 22. 2) | 0. 030\* | 3. 6 |
| Cortical BMD (Ct. BMD in mg/ccm) | 8 | 864. 2 (58. 5) | 890. 0 (41. 6) | 25. 9 (8. 1, 43. 6) | 0. 011\* | 2. 9 |
| Trabecular BMD (Tb. BMD in mg/ccm) | - | - | - | - | - |  |
| Cortical thickness (Ct. Th in mm) | 8 | 1. 20 (0. 34) | 1. 30 (0. 37) | 0. 09 (0. 002, 0. 173) | 0. 047\* | 7. 5 |
| Trabecular BV/TV (Tb. BV/TV) | 8 | 0. 174 (0. 017) | 0. 173 (0. 018) | -0. 001 (-0. 002, 0. 001) | 0. 563 | -0. 5 |
| Trabecular number (Tb. N, 1/mm) | 8 | 2. 44 (0. 38) | 2. 51 (0. 35) | 0. 06 (-0. 03, 0. 15) | 0. 177 | 2. 5 |
| Trabecular thickness (Tb. Th, in mm) | 8 | 0. 072 (0. 013) | 0. 070 (0. 011) | -0. 002 (-0. 006, 0. 002) | 0. 243 | -2. 7 |
| Trabecular separation (Tb. Sp in mm) | 8 | 0. 345 (0. 060) | 0. 336 (0. 055) | -0. 009 (-0. 023, 0. 006) | 0. 209 | -2. 6 |
| Cortical Porosity (Ct. Po) | 8 | 0. 046 (0. 028) | 0. 039 (0. 014) | -0. 007 (-0. 021, 0. 008) | 0. 315 | -15. 2 |
| Mean cortical pore diameter (Ct. Po. Dm) | 8 | 0. 154 (0. 017) | 0. 154 (0. 015) | -0. 0001 (-0. 013, 0. 013) | 0. 989 | 0. 06 |
| S | 7 | 261. 8 (20. 2) | 269. 4 (25. 8) | 7. 5 (0. 6, 14. 5) | 0. 038\* | 2. 9 |
| F. ult | 8 | 13. 1 (1. 2) | 13. 6 (1. 2) | 0. 5 (0. 1, 0. 9) | 0. 023\* | 3. 8 |
| (Tb. F/TF)dist | 8 | 58. 6 (9. 2) | 58. 5 (8. 2) | -0. 1 (-1. 5, 1. 4) | 0. 922 | -0. 2 |
| (Tb. F/TF)prox | 8 | 41. 0 (9. 8) | 39. 7 (9. 2) | -1. 2 (-2. 3, -0. 1) | 0. 034\* | -2. 9 |
| **Radius** | | | | | | |
|  | **N** | **Visit 1**  **Mean (SD)** | **Visit 3**  **Mean (SD)** | **Mean Difference**  **(95% CI)** | **P-Value** | **%**  **change** |
| Total Area (T. Ar in mm2) | 7 | 305. 0 (81. 5) | 313. 1 (91. 1) | 8. 1 (-23. 2, 39. 4) | 0. 550 | 2. 6 |
| Cortical Area (Ct. Ar in mm2) | 7 | 56. 8 (13. 3) | 61. 7 (16. 5) | 4. 9 (-1. 2, 11. 1) | 0. 099 | 8. 6 |
| Trabecular Area (Tb. Ar, in mm2) | 7 | 243. 3 (89. 9) | 250. 2 (103. 3) | 6. 9 (-23. 3, 37. 1) | 0. 596 | 2. 8 |
| Total BMD (D100 in mg/ccm) | 7 | 324. 3 (58. 8) | 344. 5 (72. 0) | 20. 2 (-3. 8, 44. 2) | 0. 085 | 6. 2 |
| Cortical BMD (Ct. BMD in mg/ccm) | 7 | 802. 1 (57. 7) | 835. 5 (67. 0) | 33. 5 (-5. 3, 72. 2) | 0. 079 | 4. 2 |
| Trabecular BMD (Tb. BMD in mg/ccm) | 7 | 183. 6 (15. 9) | 185. 3 (18. 5) | 1. 6 (-6. 4, 9. 7) | 0. 636 | 0. 8 |
| Cortical thickness (Ct. Th in mm) | 7 | 0. 81 (0. 27) | 0. 86 (0. 34) | 0. 06 (-0. 05, 0. 16) | 0. 259 | 7. 4 |
| Trabecular BV/TV (Tb. BV/TV) | 7 | 0. 153 (0. 013) | 0. 154 (0. 015) | 0. 001 (-0. 005, 0. 008) | 0. 604 | 0. 6 |
| Trabecular number (Tb. N, 1/mm) | 7 | 2. 31 (0. 17) | 2. 43 (0. 18) | 0. 12 (-0. 04, 0. 28) | 0. 119 | 5. 2 |
| Trabecular thickness (Tb. Th, in mm) | 7 | 0. 066 (0. 006) | 0. 063 (0. 005) | -0. 003 (-0. 007, 0. 002) | 0. 176 | -4. 5 |
| Trabecular separation (Tb. Sp in mm) | 7 | 0. 368 (0. 029) | 0. 350 (0. 032) | -0. 018 (-0. 043, 0. 007) | 0. 133 | -4. 9 |
| Cortical Porosity (Ct. Po) | 7 | 0. 029 (0. 018) | 0. 021 (0. 009) | -0. 008 (-0. 019, 0. 002) | 0. 110 | -27. 5 |
| Mean cortical pore diameter (Ct. Po. Dm) | 7 | 0. 140 (0. 007) | 0. 137 (0. 008) | -0. 003 (-0. 008, 0. 002) | 0. 187 | -2. 1 |
| S | 7 | 90. 7 (10. 5) | 94. 8 (9. 9) | 4. 1 (1. 3, 6. 9) | 0. 012\* | 4. 5 |
| F. ult | 7 | 4. 6 (0. 6) | 4. 8 (0. 6) | 0. 2 (0. 1, 0. 3) | 0. 004\* | 4. 3 |
| (Tb. F/TF) dist | 5 | 43. 0 (6. 4) | 44. 2 (16. 4) | 1. 2 (-12. 4, 14. 7) | 0. 823 | 2. 8 |
| (Tb. F/TF) prox | 7 | 23. 6(9. 3) | 24. 9(12. 4) | 1. 3(-3. 7,6. 4) | 0. 541 | 5. 5 |

**From visit 1-3,**

**Tibia**

Tibial Cortical area (10.1 mm2 (1.7,18.5), p=0.024), Cortical BMD (25.9 mg/ccm (8.1,43.6), p=0.011) and Cortical thickness (0.09(0.002, 0.173), p=0.047) increased significantly.

Cortical porosity decreased by 15 percent at the tibia over the 2 years (non-significant). Tibial stiffness (7.5 (0.6,14.5), p0.04) and estimated failure load (0.5 (0.1,0.9), p=0.02) increased and percentage load carried proximally at the trabecular bone decreased (-1.2(-2.3, -0.1)), p=0.003).

**Radius**

Radial stiffness (4.1(1.3,6.9), p=0.012) and estimated failure load (0.2, (0.1,0.3), p=0.004) also increased significantly.

At the radius, cortical area (8. 6%), total BMD (6. 2%), cortical thickness (7. 4%) and trabecular number (5. 2 %) all increased non-significantly.

The cortical porosity decreased by 27. 5 percent over the 2 years (non-significant).

### Discussion

#### Baseline characteristics of our cohort:

The HRpQCT parameters of a severely obese group (n=12, 5 males, mean age 15.3 (0.9) years, mean BMI 46.4 (5.6)) of adolescents have not been previously described. We sought to establish the baseline values of such a cohort and to assess changes longitudinally in HRpQCT measures at the distal radius and tibia due to rapid and significant weight loss following a 6-month intra-gastric balloon placement supported by a life style intervention programme.

In a cross sectional HRpQCT study looking at 146 males and 133 females of normal weight in 4 age categories (15, 16, 17-18 and 19-20 years, 95% post pubertal), **cortical density, cortical thickness, and total density all increased with age and contributed to an increase in the bone strength index (BSI)** in both sexes at the tibia. No significant difference was seen in trabecular microstructure, trabecular density, and BV/TV in either sex with age. Additionally in females, there was no change with total area with advancing age(332).

The study also showed that **cortical density was lower for males compared to females** at all ages, while **cortical thickness, BSI and trabecular density, and BV/TV was higher in males c**ompared to females in the 2 older age groups. Trabecular number was higher at all age groups in males across all ages.

Previous studies have shown that total area is the main contributor to bone strength in growing children, however, this study showed that once the majority of growth is complete, it is the total density that is more important.

Though there are known sex differences, we did not analyse our cohort separately due to the small numbers. Comparing the results of our cohort with this group and the centile charts showed that our baseline values were similar/higher than seen in normal weight individuals in all parameters except for *Trabecular thickness and Trabecular separation at the tibia which were lower (derived measures)(333)*

A study comparing the microstructure and strength in obese and normal weight men and women in both young adulthood and older age showed that volumetric bone density at the distal tibia was higher in obesity in both age groups and at the distal radius in the older adults. This was shown to be due to the greater trabecular density in the younger age group (30-32 years) with both trabecular and cortical density playing a role in the older age group.Trabecular density is determined by trabecular number, trabecular separation and thickness(263).

In a recent study comparing lean versus obese young people, radial cortical porosity and cortical pore diameter were lower in obese children. The obese children had thinner trabeculae but increased number in the distal tibia. The fat mass percentage correlated negatively with the radial cortical porosity (r=-0.57, p<0.001) and the radial cortical pore diameter (r=-0.38, p=0.02) and with trabecular thickness at the tibia (r=-0.39, p=0.019)

(334).

Our cohort of young people was more obese (BMI SDS 4.0 versus 3.14) and older (15.3 versus 12.6 years) than the group described.

In our cohort, total and trabecular density at the tibia (310.4 mg/ccm (54.4) and 205.4 mg/ccm (18.0)), as well as trabecular number (2.55 per mm (0.42) were higher than the means quoted in the Burrows study. That there was no impact of the lower trabecular thickness may in part be due to the higher numbers and lower trabecular separation which has also been reported in the cross-sectional study detailed above(334).

A study reviewing the microstructural changes from early to mid-late puberty at the distal radius showed no changes in the trabecular parameters in girls (similar to that seen at the tibia)(335). However, trabecular BV/TV and Tb.Th were higher through puberty in boys. However, in cortical bone, girls had lower Ct.Th and cortical BMD during mid puberty with increased markers of bone turnover while this remained stable in boys.

They were also able to evidence that temporary changes seen in cortical bone (proportion of load borne by cortical bone and the ratio of cortical to trabecular bone volume) in mid to late puberty occured at the same time as the peak that occurs in distal forearm fractures in both sexes.

A significant part of the total load carried by the skeleton is done by the Cortical bone(336). Increased cortical porosity along with other cortical defects and irregular contours can weaken the bone. How dense the cortical bone is will determine the fracture risk.(337). All cortical parameters within our cohort were above those quoted in the literature.

#### Changes after weight loss due to intra-gastric balloon removal

Bone strength and fracture risk are determined not only by bone density but also by bone microarchitecture. There is limited data in adults relating to the impact of weight loss on bone microarchitecture. In older procedures such as Biliopancreatic diversion with duodenal switch (BPD/DS), bone biopsies done in 33 patients pre and 4 years post the bariatric procedure showed decreased cortical thickness and increased trabecular bone volume alongside increased bone formation rate, turnover and mineralization. (338). Their overall conclusion was that the benefits of the procedure outweighed the risk of bone loss.

HRpQCT findings in a more recent study from 2013 showed that there is predominantly cortical bone loss (area, density, thickness and total density) after RYGB and this is seen at the weight bearing sites (tibia) and these changes were predicted by change in PTH. (339). PTH has differing impact on cortical and cancellous bone (340)and this maybe the reason that in studies where PTH has remained stable, there was no impact on lumbar spinal BMD though bone loss was seen at the tibia and hip.

A peripheral quantitative study (larger scan area (2.3 mm slice thickness) and voxel size compared to HRpQCT) looked at bone changes at 12 months in 91 obese adolescents who were randomized to standard care versus a non-surgical weight management programme. The group were younger (between 10-15 years, mean 12.2 years versus 15.3 years) than our cohort and their degree of obesity was not as severe with BMI SDS >3 excluded from the study. The 12 month change in BMI in the intervention group was -0.4 which was considered significant (BMI change -2.5 kg/m2 in our cohort). They did not find any difference in the bone outcomes (reported separately for males and females) of the 2 groups and therefore the intervention and standard care were combined for the analysis further on. (319) . They reported no changes at the tibia (trabecular vBMD, cortical vBMD, section modulus and periosteal circumference) related to change in BMI in both boys and girls. Their conclusion was that a relatively small change in BMI does not affect bone strength and density. Positive Associations were reported between lean body mass index and changes in bone though these were different based on sex and whether it was weight bearing or not (section modulus and periosteal circumference gains in radius in boys and tibia in girls).

In our cohort, the non significant increase in lean body mass seen after balloon removal positively correlated with TBLH BMD (r=0.7, p=0.02), and trabecular BMD and trabecular BV/TV fraction (r=0.77, p=0.008 for BMD and r=0.78, p=0.007) at the radius.

Our study results also showed a difference dependent on site. It seems to suggest that relatively small changes in BMI do not affect bone density or structure adversely at the tibia. Gains were seen in tibial cortical area, cortical BMD and thickness even though significant weight loss was seen at 6 months. No significant correlations with change in weight were seen at the tibia.

However, the results at the radius are less clear. **Gains were seen in total BMD, both cortical and trabecular density and trabecular BV/TV but total area decreased at the radius. Significant correlations were seen between the weight lost and trabecular number (r=-0.82, p=0.002), thickness (r=0.76, p=0.006) and separation (r=0.84, p=0.001) at the radius. Increased trabecular number, thickness and decreased separation would increase bone mineral density, therefore possible that the increased thickness had a larger role to play than the loss in number and increased separation.**

The cortical porosity also increased by 25 percent (non-significant) at the radius. Cortical porosity has an association with high bone turnover and increased risk of fracture. Increased porosity in puberty is thought to develop due to the increased calcium demand during periods of rapid growth. Forearm fractures tend to be the highest in mid to late puberty and this is thought to be due to increased cortical porosity, and an increase in cortical loading. This is unrelated to body composition. (335) We know that obese children fracture more and recent work suggests that having had a forearm fracture following mild trauma results in long term reduction in bone strength and thinner cortices(341).

We also know that higher glucose and T2DM is associated with reduced cortical porosity. (342) In our cohort, there were no children with T2DM or impaired glucose tolerance. However, nine out of the twelve had insulin resistance (elevated HOMA-IR, fasting hyperinsulinemia etc). There was a non-significant reduction post intra-gastric balloon in HOMA-IR which correlated significantly with the mean cortical pore diameter at the radius (r=-0.6, p=0.05). There was no association with the change in cortical porosity.

Precision errors related to cortical porosity in HRpQCT are quite large and a change of up to 40 percent could be needed to be considered significant. (261) Our numbers are very small, which could be the reason why the large % change in cortical porosity did not reach clinical significance.

There was no change in bone stiffness, and ultimate failure load at the radius. Recent studies have shown that it is volumetric BMD and cortical BMD, and area at the radius that is different between children that fracture compared to those who sustain a fall but do not fracture (343) though of course cortical BMD is influenced by cortical porosity. The degrees of influence of individual parameters upon each other is also difficult to clarify due to small numbers.

The decrease in total area at the radius, showed a moderate negative correlation with weight loss (r=-0.53) but the p value at 0.09 did not achieve significance. Further studies are needed to look at impact of modest weight loss on the radius and whether the increases seen in cortical porosity and the reduction in total area are of significance.

*Visit 1-Visit 3 (Baseline versus weight regain)*

Over the 2 years, gains were seen in tibial Cortical area, cortical BMD and cortical thickness with a 15 percent reduction in cortical porosity.

Significant changes were no longer seen at the radius microarchitecture and the total area (which had decreased previously) showed a non-significant increase of 2.6%.

MicroFE Analysis measures -Bone stiffness, estimated failure load increased at both the radius and tibia; however, the % load carried at the proximal end by the trabecular bone decreased at the tibia. This is difficult to explain with the increased stiffness and ultimate failure load increase but may be due to the increase % load elsewhere in the bone as the HRpQCT only captured the proximal and distal slice.

No adverse bone events were experienced between balloon removal and follow up 18 months later. The strength of bone depends on both its composition as well as its structure. Bone has to be both stiff (to resist being deformed when loaded) but also flexible to allow a certain degree of deformation without cracking(336).

Based on the centile charts, we expect to see that the bone strength across the tibia and radius should increase over the 2- year period. This is related to increase in both bone area but also BMD. Estimated Failure load (in kilonewton) based on finite element analysis was well above mean (> 90th centile) for all the young peoplewith no detriment noted at 6 months when the weight loss occurred.

Thus, based on the increase seen in stiffness and ultimate failure load seen at 2 years at the radius, the reduction in total area and increased cortical porosity at 6 months following the weight loss associated with the intra-gastric balloon placement is unlikely to be of concern.

#### Limitations:

HRpQCT can be performed only at the distal sites, thus will not give information regarding the spine and proximal sites such as the axial skeleton. Also, the site measured can change as children grow, though this can be mitigated by having a variable region of interest as reported by the Mckay group(247).

We did not separately analyze males and females due to the small numbers.

Due to the attrition rate (2/12) and problems with size, scan quality and anxiety, the numbers available for analysis were reduced further by visit 3.

The study describes a small group of young people at the extreme end of the obesity spectrum with significant co-morbidity (insulin resistance etc) which may by themselves have an impact on the bone changes seen. The young people first lost weight (10/12) but subsequently regained this (except 2/10) and were above baseline (+5.5% (14.2)) at 2 years.

This study is meant to be a pilot and therefore not powered to evaluate any differences except for BMI change. Therefore, even though some statistically significant changes have been seen, it is not possible to ascertain their clinical significance if any.

**In summary**, despite clinically significant weight loss at 6 months, tibial cortical area (2.4 mm2 (0.1,4.7), p=0.04) tibial cortical BMD (11 gm/ccm (4.1,17.9), p=0.006)

tibial Cortical Thickness (0.02mm (0.002,0.04), p=0.035) all increased as did

total BMD, (10.3 mg/ccm (0.3,21), p=0.05), cortical BMD (14 mg/ccm (8.3, 19.6), p<0.001)

trabecular BMD (4.1 mg/ccm (0.5,7.6), p=0.028) and trabecular BV/TV (0.003 (0.001,0.006), p=0.025) at the radius.

The changes at the tibia continued to show increases with age at 2 year follow up which led to an increase in stiffness, and failure load though there was a reduction in the percentage load carried by the trabecular bone at the proximal end.

The cortical porosity showed a 25 % increase at the radius at 6 months and a reduction in total area but at 2 years, this had decreased by 27.5% and the total area reduction was no longer evident. This coupled with the significant increase in stiffness and failure load suggesting that the increase (if significant) was temporary. Though, large percentage changes were seen in cortical porosity, they did not reach statistical significance which could be due to the small numbers in the study and the least siginificant change aspect of Cortical Porosity. As described in the literature, more scans had to be excluded at the radius in our study as compared to the tibia due to movement artifact and scan quality.(261)

This study is the first to describe HRpQCT measures for a cohort (albeit small) of severely obese young people (mean BMI 46.4, BMI SDS +4.0) and follow up over a 2-year period during which significant weight loss with subsequent weight gain was experienced. There is no comparable HRpCT data over time with weight loss due to an intervention such as the intra-gastric balloon. The degree of weight loss for this procedure is not comparable to that seen after bariatric procedures such as band, sleeve or bypass but falls between these and lifestyle interventions

Initial 6-month data following significant weight and BMI SDS change (-0.38, p=0.005 and -0.27(p=0.005) respectively showed gains at both the tibia and radius except for a decrease in the total area at the radius.

We do not know whether the improvement in strength parameters over the two years (as expected based on Gabel’s work) was a consequence of the weight loss or whether it would have happened anyway. Our data suggests that the young people may be gaining bone in different ways at the tibia and radius; thus, the response of weight and non-weight bearing sites to weight loss maybe different. However, the increased strength at 2 years does not reconcile with the fact that obese children and young people fracture more than their lean counter parts.

### Bone turnover markers

The balance between bone formation and bone resorption is what determines the bone mass, and bone mineralisation. The tables below outline the changes in osteokines and bone formation and bone resorption markers at the 3 time points-baseline, 6 months following weight loss due to the intra-gastric balloon placement and at 18 month follow up therafter (24 months from baseline).

The only significant change seen was decreased Urinary CTX and NTX (markers of bone resorption) at 6 months (NTX alone) and 24 months (Both CT and NTX). In a study of bone formation and turnover markers in 572 children (300 boys, between 2 months and 18 years), they were found to vary with age and pubertal stage (p<0.001) with a decline seen during late puberty and the lowest values in the transition to adulthood(344).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **RANK-L in ng/l** | | | **DKK-1 in ng/l** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 4. 68 | 4. 68 | 4. 68 | 4,961. 4 | 7,023. 6 | 6,488. 5 |
| **BOB02** | 4. 68 | 4. 68 | 4. 68 | 3,852. 8 | 7,393. 1 | 4,682. 3 |
| **BOB03** | 11. 16 | 9. 10 | 13. 16 | 7,815. 6 | 10,524. 5 | 5,508. 7 |
| **BOB04** | 9. 10 | 4. 78 | 4. 68 | 8,887. 2 | 8,036. 4 | 8,323. 7 |
| **BOB05** | 4. 78 |  | 4. 68 | 9,653. 9 |  | 5,394. 2 |
| **BOB06** | 4. 68 | 4. 78 | 4. 68 | 4,412. 5 | 6,907. 2 | 5,196. 0 |
| **BOB07** | 4. 68 | 4. 68 | 4. 68 | 5,818. 9 | 5,225. 8 | 5,146. 7 |
| **BOB08** | 4. 68 | 4. 68 | 4. 68 | 2,214. 8 | 5,113. 9 | 3,636. 2 |
| **BOB09** | 28. 16 | 4. 78 |  | 6,061. 7 | 4,495. 6 |  |
| **BOB10** | 4. 78 | 4. 68 | 60. 44 | 5,660. 2 | 5,415. 0 | 5,018. 2 |
| **BOB11** | 4. 68 | 4. 78 | 13. 16 | 5,397. 1 | 4,718. 4 | 5,149. 7 |
| **BOB12** | 4. 68 | 4. 68 |  | 8,656. 9 | 5,213. 9 |  |
| **MEAN** | 7. 56 | 5. 12 | 11. 95 | 6116. 1 | 6369. 8 | 5454. 4 |
| **SD** | 6. 83 | 1. 32 | 17. 40 | 2234. 7 | 1821. 4 | 1231. 8 |
| **P value 0-6** | 0. 23 |  |  | 0. 4 |  |  |
| **P value 0-24** | 0. 3 |  |  | 0. 5 |  |  |

Table 40 - RANK-L and DKK-1 Baseline, 6 months and 24 months

There was no significant difference between RANKL and DKK-1 at the 3 time points. (RANKL-L decreased after weight loss at 6 months and went up after weight gain at 24 months. DKK-1 went up at 6 months after weight loss but was below baseline at 24 months).

Table 41 - Change in OPG at baseline. 6 months and 24 months

|  |  |  |  |
| --- | --- | --- | --- |
| Patients | OPG in ng/l | | |
|  | **Baseline** | **6 months** | **24 months** |
| BOB01 | 49. 0 | 32. 3 | 45. 8 |
| BOB02 | 95. 5 | 86. 2 | 77. 6 |
| BOB03 | 83. 4 | 95. 2 | 55. 9 |
| BOB04 | 91. 8 | 96. 7 | 74. 2 |
| BOB05 | 102. 2 |  | 85. 1 |
| BOB06 | 76. 3 | 82. 8 | 79. 7 |
| BOB07 | 85. 3 | 68. 8 | 66. 4 |
| BOB08 | 102. 5 | 72. 6 | 67. 9 |
| BOB09 | 61. 1 | 39. 5 |  |
| BOB10 | 74. 1 | 73. 3 | 92. 9 |
| BOB11 | 74. 1 | 74. 0 | 89. 7 |
| BOB12 | 72. 4 | 76. 9 |  |
| Mean | 80. 6 | 72. 6 | 73. 5 |
| SD | 16. 2 | 20. 3 | 14. 9 |

OPG decreased after weight loss and was about similar following weight regain. Neither of these changes is significant. (p=0. 2 and p=0. 1 respectively)

#### Bone formation markers

Table 42 - Change in osteocalcin and P1NP over the 2 years (microgm/l)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Bob Pts** | **Osteocalcin** | | | **P1NP** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 33. 0 | 24. 8 | 21. 9 | 57. 6 | 50. 1 | 48. 7 |
| **BOB02** | 39. 2 | 15. 7 | 32. 8 | 93. 9 | 97. 5 | 67. 8 |
| **BOB03** | 2. 3 | 48. 1 | 30. 3 | 98. 5 | 91. 5 | 79. 9 |
| **BOB04** | 39. 1 | 64. 0 | 26. 1 | 168. 6 | 129. 4 | 77. 8 |
| **BOB05** | 21. 4 |  | 14. 5 | 138. 6 |  | 89. 9 |
| **BOB06** | 14. 2 | 29. 2 | 13. 2 | 66. 2 | 46. 6 | 40. 8 |
| **BOB07** | 16. 8 | 35. 9 | 38. 6 | 36. 0 | 43. 1 | 38. 8 |
| **BOB08** | 53. 1 | 60. 0 | 39. 4 | 84. 0 | 82. 1 | 56. 8 |
| **BOB09** | 64. 0 | 29. 9 |  | 250.0 | 250.0 |  |
| **BOB10** | 23. 4 | 55. 1 | 32. 3 | 76. 6 | 81. 0 | 56. 2 |
| **BOB11** | 31. 3 | 15. 0 | 10. 5 | 80. 8 | 79. 5 | 81. 9 |
| **BOB12** | 64. 0 | 64. 0 |  | 99. 6 | 78. 5 |  |
| **MEAN** | 33.5 | 40.2 | 26.0 | 104.2 | 93.6 | 63.9 |
| **SD** | 19.5 | 18.8 | 10.5 | 57.8 | 53.6 | 18.2 |
| **P value 0-6** | 0.5 |  |  | 0.1 |  |  |
| **P value 0-24** | 0.8 |  |  | 0 |  |  |

Osteocalcin and P1NP: No significant difference seen at different time points in the 2 bone formation markers.

(Osteocalcin increased at 6 months but was below baseline at 24 months.

P1NP decreased at 6 months with a further decrease at 24 months though none of these were significant).

#### Bone resorption markers

Table 43 - Change in urine NTX (nM BCE/mM creatinine) and CTX (µg/mM Creatinine) over the 2 years

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **CTx** | | | **NTx** | | |
|  | **Baseline** | **6 months** | **24 months** | **Baseline** | **6 months** | **24 months** |
| **BOB01** | 250.9 | 235.7 | 250.7 | 73.3 | 67.9 | 92.2 |
| **BOB02** | 178.2 | 297.6 | 99.6 | 101.8 | 95.6 | 54.5 |
| **BOB03** | 354.1 | 219.5 | 197.3 | 200.3 | 79.8 | 53.3 |
| **BOB04** | 370.4 | 304.6 | 225.6 | 215.8 | 157.6 | 69.3 |
| **BOB05** | 271.9 |  | 249.6 | 169.3 |  | 62.3 |
| **BOB06** | 274.1 | 268.7 | 163.3 | 94 | 56.8 | 40.4 |
| **BOB07** | 133.5 | 190.1 | 131.9 | 62.8 | 68.4 | 31.8 |
| **BOB08** | 251.9 | 359.6 |  | 195.5 | 116.1 |  |
| **BOB09** |  |  |  | 700.4 | 596.6 |  |
| **BOB10** | 233.6 | 264.4 | 254.1 | 153.6 | 115.4 | 63.5 |
| **BOB11** | 278.8 | 110.9 | 164.5 | 117.4 | 52.5 | 50.1 |
| **BOB12** | 396.3 |  |  | 298.4 | 238.1 |  |
| **Mean** | 272.15 | 250.12 | 192.96 | 198.55 | 149.53 | 57.49 |
| **SD** | 78.9 | 72.4 | 56.46 | 172.15 | 157.83 | 17.45 |
| **P value**  **0-6** | 0.8 |  |  | 0.001 |  |  |
| **0-24** | 0.02 |  |  | 0.003 |  |  |

There was a significant drop noted between Urine CTX at baseline and at 24 months suggesting that bone resorption decreased over the 2 years (P=0. 02). No change was seen between 0-6 months.

The Urine NTX decreased significantly (p=0. 001) at six months following weight loss and this trend persisted at 24 months despite weight regain (p=0.003).

The table below summarises the changes in the bone turnover markers seen at 6 and 24 months.

Table 44 - Direction of change in bone turnover markers over the 2 years (single arrow suggests increase or decrease, double arrow signifies change from baseline

|  |  |  |
| --- | --- | --- |
| **Bone marker** | **6/12**  **p value** | **24/12**  **p value** |
| Osteocalcin | ↑  0.5 | ⇓ (below base)  0.8 |
| P1NP | ↓  0.1 | ↓  0 |
| RANK-L | ↓  0.2 | ⇑ (above base)  0.3 |
| OPG | ↓  0.2 | ↓ (above 6/12)  0.1 |
| DKK-1 | ↑  0.4 | ⇓ (below base)  0.5 |
| Urine CTX | ↓  0.8 | ↓  0.02\* |
| Urine NTX | ↓  0.001\* | ↓  0.003\* |

#### Discussion

Both obesity and the subsequent weight loss interventions have an impact on skeletal health. Changes due to significant weight loss are manifest by changes in bone turnover markers and these may depend upon the the amount, mechanism of weight loss and type of procedure. The balance between bone formation and bone resorption is what determines the bone mass, and bone mineralisation.

The only significant change in our cohort between baseline, 6 months and at 2 years was the decrease in the bone resorption markers.

Our cohort saw a significant decline in both Urinary NTX (149.5 (157.8) at 6 months and 57.5(17.5) at 24 months from baseline 198.6(172.1), p<0.001 and <0.003 respectively) (even accounting for missing values) and CTX (250(72.4) at 6 months and 192(56.4) at 24 months from baseline 272.2(78.9), p=0.8 and p=0.02 respectively). This decline continued even at 24 months after weight was regained. The decrease in Urine NTX between visit 1-2 correlated significantly with the amount of weight lost (r=-0.69, p=0.002).

Contrary to what is seen in other adult studies, this decline could suggest that modest weight loss does not disrupt the normal reduction in bone resorption seen in late adolescence which is also evident from the stable TBLH BMD and Lumbar spine BMD during the study.

Several different studies have compared the effect of different bariatric procedures on bone mineral density and bone turnover.

In a study looking at 25 patients who underwent RYGB and 30 obese controls marched for age, gender and menopausal status, both osteocalcin (11.6±3.4 versus 7.6 ± 3.6 ng/ml, p<0.001) and urine NTX were significantly elevated (93±38 versus 24±11 nmol BCE per mmol creatinine). A subgroup was followed up for a further 9 months and this increase in bone turnover continued with associated decrease in bone mineral content(324). Other studies have shown these changes with raised osteocalcin and serum NTX persisted for 18 months (132) and raised osteocalcin and ALP, low Calcium, low Vitamin 25 (OHD) 10 years post RYGB raising conerns about metabolic bone disease even when BMI has normalised .(345)

The skeletal aspects of different procedures were compared in a small Swedish study of 19 patients (RYGB, Band, Control) found no significant changes in BMC and bone turnover markers in the gastric banding group and control group.(321)

However, Increased bone resorption as evidenced by increased C-Telopeptide has been seen 6 months after gastric banding (a restrictive procedure similarto the balloon) with this change persisting for atleast 24 months in a group of pre-menopausal obese (24-52 years, BMI 43.7, women with no evidence of secondary hyperparathyroidism.(346)

A study comparing sleeve with bypass in a group of 15 morbidly obese women, showed similar levels of increased bone turnover markers in both groups though the loss in bone mass percentage was lower in the sleeve group.(347)

The weight loss experienced in these studies was very different to our cohort with a mean BMI change of 10-17 kg/m2 versus 2.5 kg/m2 in our cohort.

We saw a non-significant rise in osteocalcin (bone formation marker) in our cohort of young people post balloon removal though this fell below baseline at 24 months. Prospective studies in obese adults could quantify the amount of weight loss needed to bring about a change in osteocalcin levels (16.8 percent), however only 8.7 percent loss in addition to regular exercise was needed to see the association between osteocalcin levels and insulin sensitivity.(348)

The change in osteocalcin we saw was positively correlated with change in truncal fat mass (r=0.66, p=0.02). Osteocalcin has a role in improving insulin resistance (349); we saw drop in basal insulin (r=0.6, p=0.05) in our cohort at 6 months. HBA1C and HOMA-IR reduced non-significantly over the first 6 months with weight loss in our study and HBA1c continued to fall at 24 months but these were not related with osteocalcin. The weight loss experienced by our cohort was lower than quoted in previous adult studies; we did not see a significant rise in osteocalcin which could be due to the smaller numbers. Links between the endocrine-bone pancreas axis through the insulin receptor on osteoblasts which stimulates release of osteocalcin have been shown in animal models where IR lacking mice had decreased bone formation and went onto develop hyperglycemia and insulin resistance.(350). In our cohort with decrease in weight and BMI SDS at 6 months, and increase in osteocalcin, significant decreases were seen in AUC insulin as well as peak insulin at 90 minutes though HOMA-IR did not improve.

A very strong positive correlation was noted between baseline and visit 2 (with weight loss) between osteocalcin and percentage load carried proximally by the trabecular bone at the tibia and change in cortical BMD at the radius (r=0.88, p=0. 004 for both) which could suggest that increased bone formation led to increased strength and bone density.

While profound weight loss such as seen after bypass has been shown to have the opposite (negative) effect, it may be that modest weight loss our cohort experienced could ameliorate obesity related detrimental changes to bone and show improvement.

OPG from the tumour necrosis factor receptor family acts as decoy for RANK-L, so when OPG falls, there is the potential for increased bone resorption due to unopposed action of RANK-L. Previous work from Sheffield has shown lower levels of OPG in obese children compared to controls with an inverse relationship with leptin and increased urine CTX (236).

In our cohort following balloon therapy, OPG levels fell (non-significant) but the bone resorption markers in our study decreased. This could be due to small numbers in our group. Change in OPG also showed a significant negative correlation with increasing ultimate failure load at the radius (r=-0.74, p=0.01), suggesting increase in bone strength.

In summary, over the 6 months that this cohort of young people experienced modest (though clinically significant) weight loss, some bone formation markers increased non-significantly (osteocalcin) and bone resorption markers (urine CTX and urine NTX) decreased significantly, suggesting that over all the balance tilted over in favour of bone formation. Some associations were seen between bone formation markers and improved strength and density as assessed by HrpQCT as well as improvements in insulin glucose metabolism. Decreased bone resorption was also evident at 2 years though this was associatd with significant weight gain.

Thus, in conjunction with the DXA results and HRpQCT findings, we can conclude that modest weight loss following intragastric balloon placement is not detrimental to bone health and may in fact reverse some of the negative effects of obesity on bone health.

In summary, our key message is that despite modest weight loss, no adverse effect was seen in bone mineral density and the young people continued to accrue bone age appropriately. There were some minor changes seen in the bone microarchitecture on HRpQCT suggesting differences at the tibia and radius (weight bearing versus non-weight bearing) and further work in larger groups over a longer period is necessary to understand these.

## Feedback/further work

The epidemic of childhood obesity has raised serious concerns both about its immediate impact as well as effect on future health.

Our project was aimed to be a feasibility study to answer the question, ‘Can we recruit to a intragastric balloon study in adolescents, can this procedure be done safely and effectively and what are the retention rates?’ In that context, the study was a success.

This study has helped to answer this question; the balloon insertion and removal procedures ran smoothly with no complications. Hospital stay was 1-2 days and there were no early balloon removals.

Of note, this trial was conducted at a tertiary Children’s Hospital with experience of performing bariatric surgery expertise available including HDU support for one of the young people who had OSA. Service specifications will need to be looked at carefully and consideration for intra-gastric balloons would need the same rigorous discussion as one would put into place for a bariatric procedure.

It is clear the IGB in adolescents is effective in the short term. However, the magnitude of weight loss is much smaller than compared with bariatric surgery. The pros and cons of a temporary, reversible procedure which is less effective than bariatric surgery in this severely obese population with limited availability of interventions, but still necessitates a hospital stay/side effects/ complication risk needs to be weighed up against a permanent procedure with limited long term data. This is now changing with several bariatric studies reporting longer term data.(73)

Feedback so far from the participants in the project has been positive. Even the ones who lost only a small amount of weight or none, suggest that they have benefitted from taking part. It has given them the confidence that they can lose weight if they put their mind to it(248).

However, they all felt that the formal support provided should have been longer and that the 6-8 months built into the protocol was not enough. However, at the same time engagement with the lifestyle intervention steadily declined with more appointments attended in the first 3 months than in the last 3 months. 9/12 young people did not live in Sheffield and this had a significant impact on the number of sessions attended.

We have previously discussed reasons for this; the distance involved, limited parking (even though all travel expenses were reimbursed, there was no recompense for time off work for the parents). Though, we tried to be as flexible as possible for the lifestyle intervention and tried to fit appointments around the young person and their family, the days when 2 appointments had to be attended (to see the doctor and the exercise and science officer) were particularly difficult. In retrospect, these should have been at the same place unless a specific medical test was needed which could only be done at the hospital. Options to deliver the lifestyle intervention at local gyms were considered but some of the young people were too young, and some too self-conscious to consider this. Going forward this maybe an area to address – locality provision (which was in fact what we had stated in the protocol but failed to deliver this for logistical reasons) and improved engagement with the exercise programme.

For us as a team, it was immensely satisfying to be able to offer a reversible treatment to the young people who were unhappy and frustrated and felt there was no support out there for them. However, expectations regarding the balloon varied with many assuming the balloon would ‘do the job’ for them without any significant change on their part. The fact that the balloon was only a mode to ‘kick start’ the weight loss was emphasized on more than one occasion.

Though a 4-week preparatory phase was built into the study, perhaps this should be longer to ensure that the young people and parents fully understand the commitment involved in taking part.

The young person who has been the most successful in the project at losing the maximum amount of weight felt that the lifestyle intervention should have continued weekly for the entire duration of the project rather than be phased out 2 months after the balloon came out. This was planned with the aim to make the young people and their families more independent in making lifestyle choices after empowering them with the skills to do so.

A National Institute of Health sponsored workshop on the development of the precision medicine approach to tackling severe obesity in adolescents reported that the aetiology of severe obesity was heterogenous which explained the differential impact of obesity interventions. They also acknowledged that substantial gaps existed in understanding the biological, psychosocial and behavorial elements driving the obesity and that these were likely to play a role in treatment response(351).

Therefore, it can be difficult to get the balance right for some young people between being prescriptive or encouraging self management after a period and more research is needed to tailor care to individual families and young people.

General trend is disappointing longer term and seems to be worse when compared to adults with subsequent weight gain once the balloon is removed. In adult studies though weight regain was noted at one year, they had still maintained 27 percent excess weight loss)(97). The reasons for this could be related to motivation, ability to make independent food choices and lower baseline weights.

Data on changes in gut hormones, osteokines, bone formation and resorption markers, bone architecture before and after weight the loss is novel but the numbers are too few to draw any definite conclusions. Reassuringly, no negative impact was seen on bone mineral density or bone mineral content following weight loss at a time when accrual of bone mass is crucial.

Further work could look at doing an RCT comparing a more systematic/ structured lifestyle package with an intragastric balloon plus lifestyle intervention.

A similar RCT in Australia for which some preliminary data has been presented was similar to ours and showed that any weight loss followed by the balloon was not maintained longer term. (352). In this study, 12 adolescents were randomized to lifestyle alone or lifestyle plus balloon group. These participants were younger than our cohort and less heavy (BMI Z score of 2.45-2.7). After the intensive 10-week phase, significant weight loss was seen in both groups, however this was not maintained at six months. The intervention group showed a significant reduction in BMI z score at 6 months (-0.17±0.13, p=0.043). There is also a possibility that the role of the intra-gastric balloon may get restricted to preparing young people by reducing their anaesthetic risk and assessing their compliance to lifestyle intervention before proceeding to bariatric surgery. This is similar to its use in adults where the main role may be for those who are not keen on surgery or prior to proceeding to permanent bariatric surgery(353)*.*

Conventional IGB treatments being converted to adjustable balloons by systematically increasing the amount of saline injected based on weight loss are also an emerging therapy. One case was described where 2 adjustments were made with additional 160 and 180 ml of normal saline injected into the balloon. The patient lost 10 percent body weight with a reduction in BMI of 3.6 kg/m2. The safety and side effects profiles are yet to be reported for adjustable balloons*(354).*

The other option considered is the endosleeve procedure that has shown excess weight loss of up to 23. 6 percent at 12 weeks in the first published report related to its use (12 patients, 5 men, BMI 43 kg/m2, 2 early removals, no significant adverse effects). The endobarrier is an endoscopically and fluoroscopically inserted implant that is reversibly fixated to the duodenal bulb and extends about 80 cm into the small bowel allowing transit of chime from the stomach to the jejunum without contact with the duodenal wall thus mimicking a duodenal-jejunal bypass and bringing about weight loss through malabsorption(355).

The first feasibility study looking at 6 adolescents has shown some benefit in both weight loss (mean 20. 8 % at 6 months) and improved metabolic profile. These young people were young adults with a mean age of 18 (range from 16. 1 to 19. 3), a mean BMI of 44. 7 that is lower than our population (356). However, only 2 subjects completed 6 months of treatment, the reasons for which are unclear, therefore it is difficult to draw any conclusions of the feasibility and efficacy of the endobarrier based on this. More recently, the clinical trial in the US had to be terminated prematurely because of the increased incidence of liver abscesses that crossed the threshold of 2 % amongst participants(357). This will therefore not be an option available in the foreseeable future (7 cases of hepatic abscess with a 3.5 % incidence).

The option of bariatric surgery for adolescents is well established in the United States but still in its infancy in the UK with only Sheffield, Bristol and London currently undertaking this. We have recently described the youngest cohort in the UK to undergo bariatric surgery and service specifications are now in place for centres who seek to exercise this option. (77)

However, GPs in the UK continue to be sceptical about the benefits of bariatric surgery especially in the paediatric population. In a survey of 534 invited GPs, 184 responded. Only just over half of these were referring severely obese children to combined life style interventions and though two thirds knew that bariatric surgery could be effective in this patient cohort, only 41 percent said they would consider referral for surgery due to concerns about long term efficacy and safety. (358)

Three quarters of all adult bariatric surgery takes place in the National Health Service, referrals for this are still made in primary care.(359). Longer term studies looking at obesity interventions and comparing both clinical and cost effectiveness as well as improved communication and education are needed to reassure family practitioners.

A study looking at the cost effectiveness of adolescent bariatric surgery used the published results of 228 patients from the TEEN LABs group. They assumed that in the no surgery group, participants remained the same weight (which is unlikely given weight trajectories), while the bariatric surgery group were subjected to the risks of initial morbidity following the procedure, plus the complication and mortality risk but also the Qol improvement seen longer term following weight loss.

A willingness to pay threshold of $100,000 was used to look at cost effectiveness. The analysis found that owing to the initial cost and morbidity, bariatric surgery was cost effective only if assessed over five years. (360)

A similar analysis in the UK with much smaller numbers (18 patients) showed that the incremental cost/Quality Adjusted Life Years (QALY) for RYGB was on average £2011 and £1960 for sleeve gastrectomy. They concluded that bariatric surgery was cost effective but more costly than the no surgery option but there was a significant improvement in quality of life for those who underwent surgery.(361)

There were no papers looking specifically at the cost effectiveness of the intragastric balloon in severe adolescent obesity. The procedure and associated costs are lower than bariatric surgery, however the extent of weight loss is far lower and enough data is not available in terms of follow up weight loss to be able to draw any conclusions.

There continues to be big lacunae in effective interventions tailored towards the severely obese young people and ours is the first study of its kind exploring the potential of the balloon in some of the youngest and most severely obese young people.

Further research is needed to look at why the balloon seemed to be less effective in young people when compared to adults (Mean weight loss of 7 kg versus 17. 8 kg)(83), what levels of obesity and which age group are likely to benefit most.

We also need to consider how intense the dietetic and lifestyle intervention need to be while still affording flexibility. For example, a 10 month 5 days a week programme in the setting of an institution with exercise, dietary input and psychological support in 26 severely obese adolescents (mean BMI 33.9 kg/m2) showed results like the balloon in adults (mean weight loss of 16. 9 kg ±1. 3 kg), far excess of what we saw in our study(326). However, one would need to consider whether a 5-day week programme (essentially everyday) is realistic both to deliver and attend for young people.

We can also learn from the 2 families and young people who maintained and continue to lose weight-what were the differences/similarities between them? Are there any characteristics we can identify that helped them to succeed?

Several studies have looked at factors that predict success in a weight loss programme including adherence and attrition rates.

In a study of adolescents in a bariatric surgery program where they were divided into completers versus non-completers (those that withdrew from the programme during the preoperative phase), more females and younger adolescents underwent bariatric surgery. While the expectation at the start was that family and psychosocial aspects would be the determinants, it was the demographics that significantly predicted uptake(362). However, in contrast in Cohen’s study which explored the association between adolescent psychological functioning and completion of the pre-operative phase of a bariatric surgery programme with adjustment for demographics and BMI, both parents and the young people in the non-completers (about 42 percent, similar to adult studies) reported significantly more emotional problems, and poor personal adjustment. (363)

There is very little qualitative work on the patient’s motivation for bariatric surgery, how they make this decision and their experiences. A 60-minute semi structured interview of 7 young people aged 16-21 years (5 post–operative) conducted in the USA showed that the decision to proceed with bariatric surgery is not taken lightly and comes after a long journey of obesity and multiple unsuccessful weight loss attempts since childhood. (364)

In the UK, NICE recommends bariatric surgery in adolescents in ‘exceptional circumstances’, though the definition of these circumstances can be interpreted differently. The in depth analysis of 5 adolescents who underwent bariatric surgery (between 16-18 years) and 4 of those who were considering it revealed that young people are willing to accept surgery as a last resort option though there are a lot of dilemmas around it as they feel nothing better is available. (365)

The above studies show that a decision to undergo bariatric surgery is taken following significant deliberation by the young people and that age, gender, and psychosocial aspects all have a role in determining those who decide to go ahead with it eventually.

Most young people who go ahead with it seem happy with their decision to do so even though it is a difficult time. (366)

Worries were related to uncertainity regarding contacts from the health care team and the eventual transition to primary care though one may argue that given the limited long term data in this group of young people, hospital secondary care follow up may be more appropriate.

A thorough medical and psychosocial assessment with plenty of time for discussion should be a prerequisite for any adolescent bariatric/balloon programme.

Also, given the emotive nature of the subject, any intervention particularly surgical (even if temporary) leading to rapid weight loss raises concerns about impact of these on growth, incidence of eating disorders, bone and mental health. This is as it should be for children and young people but while the scrutiny is appropriate and essential, it should not result in diluting the efficacy of the intervention.

A key weakness of the project includes the absence of a control group. While this was, PPI driven (who felt recruitment to a normal care group would have been very difficult),

a design with a delayed intervention would have been far better. We have used the young people’s previous weight trajectory as a comparator as one of the inclusion criteria was prior participation in a community based health project.

However, having a control group would have been far more powerful. Even weight maintenance for 6-12 months is a worthwhile aim in severely obese young people who have essentially exhausted all other options. 2/10 continued to lose weight (20 percent) which is comparable to some other lifestyle intervention studies. However, clearly, there is no comparison with the weight loss sustained during bariatric surgery and this should be made clear to families at the outset(71).

This cohort experienced a 20 kg mean weight gain seen in the two years preceding the study; even the modest weight loss/no weight gain experienced in the 6 months that the balloon was in situ was a positive outcome.

In summary, the intra-gastric balloon has been found to be safe, well tolerated and effective in the short term in bringing about modest weight loss in a feasibility study involving 12 severely obese young people(367). There was clinically important improvement in co-morbidities, albeit short- term in most instances. There was no detrimental effect on bone of rapid weight loss in adolescents.

In my opinion, the intragastric balloon intervention was effective as we could show weight loss in cases previously resistant to losing weight, and of these 20 percent were able to show sustained weight loss over longer term. If we can assess a family’s motivation to change, and improve the compliance with the support programme, and include this as a part of their assessment pre procedure (as shown in a number of studies described above), chances of long term weight loss with sustained life style change is likely.

While the technique was safe and effective, a larger RCT and more qualitative work to hone in on the markers of success with this intervention would be needed to fully evaluate clinical benefit and cost effectiveness.

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# Appendix

**Appendix 1 - BOB Source Data**

**Patient 1**

**Screening process- Prior to consent**

Approach: Telephone/advertisement/other

Date and Time:

Spoken to whom and by:

Signature:

**Initial face to face discussion**

Date and Time-

Persons present-

Signature-

Details-

Questions asked and clarified-

Saw MT/DIC- Yes/No

Saw LR- Yes/No

**Medical/Surgical History**

Fracture history

**Screening Check list for eligibility for BOB study: -**

**Completed by**

**Date/time and signature**

Weight

Height

BMI BMI SDS BMI Centile

BMI ≥ 3.5 SD for age and sex- Yes/No.

**Tanner Stage of Development**

Stage I 🞎

Stage II 🞎

Stage III 🞎

Stage IV 🞎

Stage V 🞎

Bone age done-Yes/No

>15 for boys and 13 for girls

Previous gastric surgery- Yes/No

Congenital GI anomalies –Yes/No

Motivation to lose weight - Yes/No (expresses strong desire to lose weight, has tried community weight management programme/diets/hospital dietetics/medical treatment).

Pregnancy test- Yes/No

Willing to avoid pregnancy for at least 1 year post procedure- Yes/No

(discussion with young person and carer).

Willing to adhere to nutritional guidelines post operatively- Yes/No

(discussion with young person and primary carer.)

Carer can give informed consent- Yes/No

Patient can give meaningful assent- Yes/No

No major pre-existing psychiatric morbidity - Yes/No

(Not on medication; no history of eating disorders; no history of self harm as assessed by history and patient notes).

**Patient eligible for study- Yes/No**

Patient information leaflets given/posted-

By/To-

Date and Time-

Signature-

Any further discussion-telephone/face to face

**Consent process**

**Informed Consent**

Consent form date & version number \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date informed consent signed \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Assent form date & version number \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date assent form signed \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Consent taken by \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature, Date and time \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Study was discussed with parent/guardian 🞎

Consent form in site file 🞎

Copy of consent in SCH clinical notes 🞎

Copy of consent form given to parent/guardian 🞎

Letter sent to GP 🞎

**Demographic Data**

Date of Birth \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Gender \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ethnicity \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Lifestyle and Exercise Overview Package**

**Contact with the dietician-when/where/how long**

**Food diary given**

**Date and Time**

**Food diary returned**

**Date and Time**

**Questionnaires**

CY-PSPP completed – Yes/No

Date and Time

PedsQL completed- Yes/No

Date and Time

Assessment of Planned Behaviour completed- Yes/No

Date and Time

Physical Activity Questionnaire completed-Yes/No

Date and Time

Assessment by modified Balke protocol-Yes/No

Date and Time

Results- not sure how the results would be displayed?

Lindsey contacts:

**Pre-balloon medical Assessment**

**Visit 1**

Date \_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg Details of instrument used. Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg Average of 3 readings/RUL

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

BMI

BMI SDS/Centile

Urine Pregnancy Test Lot Number \_\_\_\_\_\_\_\_\_\_\_\_

Result (Neg/Pos) \_\_\_\_\_\_\_\_\_\_\_\_

Cannula 🞎 Results

Bloods…

FBC 🞎

U & Es 🞎

LFTs 🞎

Bone Profile 🞎

Vit A & D & E 🞎

F Insulin/Glucose 🞎

Lpt/Adiponectin 🞎

OPG/DKK1/RANKL 🞎

Ghrelin 🞎

Osteocalcin 🞎

P1NP 🞎

Urine CTx 🞎

GLP (5) 🞎

GIP (5) 🞎

All samples obtained Y/N \_\_\_\_\_\_\_

Details

Time to Lab \_\_\_\_\_\_\_\_\_

Time BM in centrifuge \_\_\_\_\_\_\_\_\_

Aliquot sample time \_\_\_\_\_\_\_\_\_

Time into -80 freezer \_\_\_\_\_\_\_\_\_

OGTT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 0 min | 30 min | 60 min | 90 min | 120 min |
| Glucose |  |  |  |  |  |
| Insulin |  |  |  |  |  |
| GLP |  |  |  |  |  |
| GIP-1 |  |  |  |  |  |

**Scans**

DEXA

Date/Time \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Performed by

Bone Age

Date/Time

Performed by

HRpQCT at NGH

Date/Time\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Transport

Performed by

**Visit 2**

Date of Admission \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Consent for procedure \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date and Time

Consent for anaesthetic \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date and Time

Date of Surgery \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Performed by

Ward admitted

Date of Discharge \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Details of procedure \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Any complications \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Medication prescribed \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ By

GP notified to rpt \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ By

Card with contact details \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Information in notes \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Written by

Symptom diary given \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Dietetic Advice given \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Side effects/adverse events symptoms explained \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Letter for school

Letter for A&E

Phone call day after discharge \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date/Time

Log of any other contacts

**Expected side effects-**

Nausea, bloating, abdominal discomfort and diarrhoea and cramping. These side-effects are temporary and normal. Medication will be given to help with these.

**Adverse events-**

Ulcer

Early removal due to side effects

Deflation of balloon which passes out naturally without causing obstruction

**Serious adverse events-**

Gastric obstruction

Gastric perforation

Death

**Visit 3 (1wk post op) (Day either side)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_

Bloods

U & Es 🞎

Sample Obtained 🞎

Time to lab \_\_\_\_\_\_\_\_\_\_

Symptom diary reviewed?

By

Date and Time

Assessment: ask about nausea/vomiting/abdominal discomfort

Any complications?

Medication-

**Visit 4 (2wk post op) (Day either side)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_

Bloods

U & Es 🞎

Sample Obtained 🞎

Time to lab \_\_\_\_\_\_\_\_\_\_

Symptom diary reviewed?

By

Date and Time

Assessment: ask about nausea/vomiting/abdominal discomfort

Any complications?

Medication

**Visit 5 (3wk post op) (Day either side)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_

Bloods

U & Es 🞎

Sample Obtained 🞎

Time to lab \_\_\_\_\_\_\_\_\_\_

Symptom diary reviewed?

By

Date and Time

Assessment: ask about nausea/vomiting/abdominal discomfort

Any complications?

Medication

**Visit 6 (4wk post op) (Day either side)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_

Bloods

U & Es 🞎

Sample Obtained 🞎

Time to lab \_\_\_\_\_\_\_\_\_\_

Symptom diary reviewed?

By

Date and Time

Assessment: ask about nausea/vomiting/abdominal discomfort

Food diary given- Yes/No

By

Date/Time

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg (document machine used)

Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg (average of 3 readings/RUL)

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

Complications

Medication

**Lindsey contacts**

**Visit 7 (2/12 post op)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg

Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mm hg

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

Food diary returned

By

Date/Time

Complications

Medication

**Lindsey contacts-4 (1/week)**

**Visit 8 (3/12 post op)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg (Document machine used)

Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg (average of 3 readings /RUL)

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

Complications

Medication

**Lindsey contacts-4 (1 per week)**

**Visit 9 (4/12 post op)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg (Document machine use)

Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg (average of 3 readings /RUL)

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

Complications

Medication

**Lindsey contacts 4-1 per week**

**Visit 10 (5/12 post op)**

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg (Document instrument used)

Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg (average of 3 readings /RUL)

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

Complications

Medication

**Lindsey contacts 1/week-4**

**Visit 11 (6/12 ) Balloon removal**

Date of Admission \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Consent for procedure \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date and Time

Consent for anaesthetic \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date and Time

Date of Surgery \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Performed by

Ward admitted

Date of Discharge \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Details of procedure \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Any complications \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Card with contact details \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Information in notes \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Written by

Symptom diary given \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Dietetic Advice given \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Given by

Phone call day after discharge \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date/Time

Log of any other contacts

**Lindsey contacts**

**Post balloon assessment (Visit 12) (within 2 weeks of balloon coming out)**

Date \_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg Details of instrument used. Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg Average of 3 readings/RUL

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

BMI

BMI SDS/Centile

Symptom diary reviewed?

By

Date and Time

Assessment: ask about nausea/vomiting/abdominal discomfort

Urine Pregnancy Test Lot Number \_\_\_\_\_\_\_\_\_\_\_\_

Result (Neg/Pos) \_\_\_\_\_\_\_\_\_\_\_\_

Cannula 🞎 Results

Bloods…

FBC 🞎

U & Es 🞎

LFTs 🞎

Bone Profile 🞎

Vit A & D & E 🞎

F Insulin/Glucose 🞎

Lpt/Adiponectin 🞎

OPG/DKK1/RANKL 🞎

Ghrelin 🞎

Osteocalcin 🞎

P1NP 🞎

Urine CTx 🞎

GLP (5) 🞎

GIP (5) 🞎

All samples obtained Y/N \_\_\_\_\_\_\_

Details

Time to Lab \_\_\_\_\_\_\_\_\_

Time BM in centrifuge \_\_\_\_\_\_\_\_\_

Aliquot sample time \_\_\_\_\_\_\_\_\_

Time into -80 freezer \_\_\_\_\_\_\_\_\_

OGTT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 0 min | 30 min | 60 min | 90 min | 120 min |
| Glucose |  |  |  |  |  |
| Insulin |  |  |  |  |  |
| GLP |  |  |  |  |  |
| GIP-1 |  |  |  |  |  |

**Scans**

DEXA

Date/Time \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Performed by

Bone Age

Date/Time

Performed by

HRpQCT at NGH

Date/Time\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Transport

Performed by

Lindsey weekly contacts for another 8 weeks after balloon comes out.

**Food diary given –by LR**

**Date and Time**

**Food diary returned**

**Date and Time**

**Session with dietician-where/when/whom/how long**

**Questionnaires**

CY-PSPP completed – Yes/No

Date and Time

PedsQL completed- Yes/No

Date and Time

Assessment of Planned Behaviour completed- Yes/No

Date and Time

Physical Activity Questionnaire completed-Yes/No

Date and Time

Assessment by modified Balke protocol-Yes/No

Date and Time

Results-

**Visit 13 (12 months post balloon insertion)**

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg Details of instrument used. Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg Average of 3 readings/RUL

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

BMI

BMI SDS/Centile

**Questionnaires**

CY-PSPP completed – Yes/No

Date and Time

PedsQL completed- Yes/No

Date and Time

Assessment of Planned Behaviour completed- Yes/No

Date and Time

Physical Activity Questionnaire completed-Yes/No

Date and Time

Assessment by modified Balke protocol-Yes/No

Date and Time

Results-

**Visit 14 (18 months post balloon insertion)**

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg Details of instrument used. Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg Average of 3 readings/RUL

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

BMI

BMI SDS/Centile

**Questionnaires**

CY-PSPP completed – Yes/No

Date and Time

PedsQL completed- Yes/No

Date and Time

Assessment of Planned Behaviour completed- Yes/No

Date and Time

Physical Activity Questionnaire completed-Yes/No

Date and Time

Assessment by modified Balke protocol-Yes/No

Date and Time

Results-

**Visit 15 (24 months post balloon insertion)**

Date \_\_\_\_\_\_\_\_\_\_\_\_

Ametop Y/N \_\_\_\_\_\_\_\_\_\_\_\_

Time \_\_\_\_\_\_\_\_\_\_\_\_

Weight \_\_\_\_\_\_\_\_\_\_\_\_kg Details of instrument used. Height \_\_\_\_\_\_\_\_\_\_\_\_cm

Blood Pressure \_\_\_\_\_\_\_\_\_\_\_\_mmhg Average of 3 readings/RUL

Waist Circumference \_\_\_\_\_\_\_\_\_\_\_\_cm

BMI

BMI SDS/Centile

Urine Pregnancy Test Lot Number \_\_\_\_\_\_\_\_\_\_\_\_

Result (Neg/Pos) \_\_\_\_\_\_\_\_\_\_\_\_

Cannula 🞎 Results

Bloods…

FBC 🞎

U & Es 🞎

LFTs 🞎

Bone Profile 🞎

Vit A & D & E 🞎

F Insulin/Glucose 🞎

Lpt/Adiponectin 🞎

OPG/DKK1/RANKL 🞎

Ghrelin 🞎

Osteocalcin 🞎

P1NP 🞎

Urine CTx 🞎

GLP (5) 🞎

GIP (5) 🞎

All samples obtained Y/N \_\_\_\_\_\_\_

Details

Time to Lab \_\_\_\_\_\_\_\_\_

Time BM in centrifuge \_\_\_\_\_\_\_\_\_

Aliquot sample time \_\_\_\_\_\_\_\_\_

Time into -80 freezer \_\_\_\_\_\_\_\_\_

OGTT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 0 min | 30 min | 60 min | 90 min | 120 min |
| Glucose |  |  |  |  |  |
| Insulin |  |  |  |  |  |
| GLP |  |  |  |  |  |
| GIP-1 |  |  |  |  |  |

**Scans**

DEXA

Date/Time \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Performed by

HRpQCT at NGH

Date/Time\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Transport

Performed by

**Food diary given**

**Date and Time**

**Food diary returned**

**Date and Time**

**Questionnaires**

CY-PSPP completed – Yes/No

Date and Time

PedsQL completed- Yes/No

Date and Time

Assessment of Planned Behaviour completed- Yes/No

Date and Time

Physical Activity Questionnaire completed-Yes/No

Date and Time

Assessment by modified Balke protocol-Yes/No

Date and Time

Results-

**Appendix 2 - Booklet for gastric BALLOON**

**Appendix 3a - Parent Information Sheet**

**Study title**

**A feasibility study of the acceptability and efficacy of intra-gastric balloons for the treatment of severe adolescent obesity and the metabolic and psychosocial effects of weight loss- called the BOB study or the Balloons in Obesity Study**

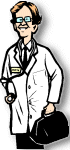
**Part 1 – to give you first thoughts about the project**

1. **Invitation paragraph**

You and your child are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you and your child if you take part.

Part 2 gives you more detailed information about the conduct of the study.



Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you want your child to take part.

1. **What is the purpose of the study?**

The purpose of the study is to see if a special balloon placed in the stomachs’ of severely overweight young people (13-16 years) for 6 months, together with diet and exercise can help them lose weight and keep the weight off for at least 18 months.

**2.1 What are the risks of being overweight?**

Body mass index (BMI) is used routinely by health professionals as a measure of a person’s weight against their height to decide if they are overweight, normal weight or underweight. A BMI greater than 30 is classed as obesity and over 40 as ‘morbid obesity’ in adults. In children, BMI varies with age as they are still growing.

A small number of children and young people (about 3 in every 10,000) have weights around 90-150 kg (14-24 stone) or more. This is equal to a BMI of 40 in adults.

These young people can have health problems because of their weight while they are still young and also have a greatly increased risk of developing diabetes and high blood pressure later on in life. Research suggests that worries about their weight can affect these children’s quality of life. Very obese children are more likely to suffer from low self esteem, depression and poor school attendance.

* 1. **What do we know about weight loss and balloons?**

Placing a balloon in the stomach (intragastric balloons or stomach balloons) has been used to help people lose weight for 25 years. They work by reducing the size of the stomach so that the person feels full sooner and therefore eats less food. Research in adults has shown weight loss of about 3 stone with them but because people tend to put on weight after the balloon is removed, permanent weight loss surgery is preferred in adults.

We think balloons may be more effective and acceptable in young people for several reasons:

**a) They are safer**

Doctors have tried many different things to help young people lose weight but many children do not find this helpful. Their weight can reach a point where a weight loss surgery (like stomach banding or bypass) becomes a consideration. However, there is concern about using this in children, as it is permanent and has significant risks associated with it.

We are not suggesting the use of stomach balloons in children with moderate overweight problems where diet and exercise is the best option.

The plan is to use the stomach balloon in young people who are severely overweight and already at high risk of health related complications because of their weight and may otherwise be considered for surgery.

Balloons are a temporary treatment –they stay in for only 6 months and the complications are much fewer when compared to weight loss surgery. The risk of death is much less as well (7 in 10,000 versus 100 in 10,000 for weight loss surgery)

**b) Children are more able to change their habits**

Balloons offer a temporary way (stay in for 6 months) of promoting weight loss, however once the balloon is removed we believe young people are more likely to continue with new eating and exercise habits than adults, and as a result weight loss is more likely to continue.

**c) There has been a small amount of research to say they work in young people**

A small number of research studies have shown the balloon does work in helping young people to lose weight. However, only a few studies have continued to measure weight loss once the balloon is removed. Many of these studies did not use a diet and exercise programme run by trained professionals either.

We want to find out how much weight young people lose with the stomach balloon and whether they continue to lose weight or put weight on again in the 18 months after the balloon is removed. We also want to look at how the weight lost helps young people in their day to day lives with school, physical activities and friends.

**3.0 What are we going to study?**

We want to study a number of different things:

a) Weight loss in the 6 months that the balloon is in the stomach

b) Is weight loss maintained for up to 18 months after the balloon is removed?

c) Does weight loss improve the young person’s quality of life?

d) What impact does the procedure have on how your child feels about their friendships as well as school life and their physical fitness?

e) Does weight loss improve their long term health? We will study the impact on blood pressure, cholesterol levels, liver function and how the body handles a load of sugar.

f) Does losing a large amount of weight quickly affect the growing bones?

**4.0 Why has my child been chosen?**

Your child has been invited to take part because their doctor thought that they would be suitable for the study based on their measurements. We think the programme will be of benefit to both you and your child both, in losing weight and also in leading a healthier life style. We are only considering young people who have tried all other options to lose weight.

Our study aims to look at the effects of the stomach balloon in combination with a diet and exercise programme in 12 very obese young people (changed from morbidly obese) who have tried to lose weight by other means.

**5.0 Does my child have to take part?**

No. It is up to you and your child to decide whether or not to take part. You are both free to withdraw from the research at any time and without giving a reason. Your decisions about this will not affect the standard of care your child will receive.

If you are happy to take part, and are satisfied with the explanations from the research team, you will be asked to sign a consent form. If your child is happy to take part, they will be asked to sign an assent form. You will be given a copy of the information sheet and the signed consent/assent forms to keep for your records.

**6.0 What will happen to my child if we agree take part?**

A short summary of what will happen to your child is outlined below, please remember at any time if you want to ask us a question, we are here to help and explain.

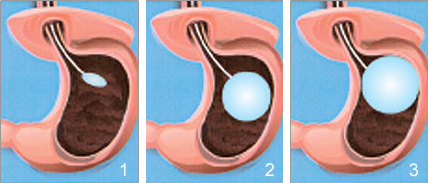
* There will be an initial meeting to make sure that the project is right for your child, to answer any questions you or your child may have and take consent for the study.
* Doctors will use a ‘camera’ to place a balloon in the stomach. It takes 20-30 minutes and your child will be put to sleep to do it using a general anaesthetic. The balloon will stay in for 6 months and your child will again be put to sleep to remove it.
* The project will involve blood tests, urine tests and bone x-rays (changed from scans) before the balloon goes in and after it comes out to look at the how weight loss affects your child’s general health and bones.
* Your child will also have their height, weight measured monthly for the 6 months the balloon is in.
* We also want to find out how weight affects the quality of life of the young people. We will assess the effects on their quality of life (self confidence, friends, school and physical activity) by asking them to fill out questionnaires
* Your child will also attend a weekly support session run by the exercise science officer from Hallam University where they will talk through different areas of their life, receive food and physical activity advice as well as participate in some physical activity. This will be at a sports centre near where you live or at Hallam University.
* There will also be monthly home visits by the exercise science officer the month before the balloon goes in, while it is in and in the month after the balloon comes out.(total 8 visits)
* **At 3months whilst the balloon in (halfway stage) and 6 months after the balloon has been removed, you will take part in an informal discussion group with a member of the research team. The aim of this is to understand what the project is like from your perspective, what works well and not so well, allowing you the opportunity to give feedback to inform future potential studies.**
* A flow chart to explain how the study will progress is included in this information sheet.
* Your child will not be able to take part if they are pregnant. One of the criteria for the study would be for them to agree to not get pregnant for at least one year after the balloon comes out. If they did fall pregnant while the balloon was in, the balloon would be removed as soon as possible as we do not know if it is safe to leave it in in pregnancy. We will be asking all sexually active girls to have a pregnancy test (on urine) at the start of the study, after the balloon comes out and again at 18 months when we do the final follow up. This is to make sure that it is safe for them to have the bone x- rays.

*6.1.* **How are balloons put in and taken out?**

The balloons will be put in by a children’s doctor who is a gut specialist. The anaesthetic medicine to put your child to sleep will be given through a cannula (thin, plastic tube) in a vein in their arm and this area will already have been made numb using ‘magic cream’ or local anaesthetic. You are welcome to be with your child when they go to sleep and again when they are waking up. Your child will be asked not to eat or drink anything for 12 hours before the procedure.

The gut specialist will use a thin plastic tube with a camera at one end (surgical instrument like telescope removed) to put the balloon in and this will take between 20-30 minutes. The balloon will be filled with salt water and left in for 6 months. The balloon will be removed in exactly the same way six months later. The balloons are made of a silicone material so they will not burst.

Your child will usually be able to go home the same day once they have recovered from the procedure and had something to drink. However, if they are being sick, we may keep them in hospital overnight. They will need to rest for 1 day after the balloon goes in and again after it comes out. They may need to rest for longer.

****

**This is how the balloon looks when put in the stomach**

For the first 3 days after the balloon goes in, your child will be on a liquid diet (things like juices, thin soups, jelly and milk) with instructions to drink lots of water. After that, the dietician will recommend puree foods for a further 3 days before moving onto soft and then solid foods.

Your child must drink plenty of fluids all the time the balloon is in place. They will be on an oral medicine to help reduce acid reflux for the 6 months that the balloon stays in.

We will do a weekly finger prick blood test in the first month (4 times) after the balloon goes in to make sure that we do not upset the salt balance of the body. We will also see your child monthly (4 more visits) in the 6 months that the balloon is in to measure their height and weight and find out how they are getting on.

**6.2 How will we measure the changes that take place?**

We will find out what changes have taken place by doing tests before the balloon goes in and after it has come out

To find out how much weight they have lost, we will measure your child’s height and weight .

To find out how their health has improved, we will measure their blood pressure, liver enzymes, and kidney function and vitamin and cholesterol levels.

We will also do a test called Oral glucose tolerance test (OGTT for short) to find out how the body deals with a sugar load. A small hollow plastic tube (cannula) will be placed in a vein in the arm/hand and this will be bled back like a tap for blood tests every 30 minutes over a 3 hour period. The back of the hand will be made numb by using an anaesthetic cream before the cannula is put in.

It is important not to have anything to eat after midnight the previous day before the test though they can have water.

The blood tests will involve taking a total of 21.5 ml of blood each time-a little more than 1 table spoon.

To find out how being overweight affects your child’s life, we will ask them to fill 3 questionnaires looking at issues like their school life, ability to participate in P.E, friendships etc. We will ask them to fill out these questionnaires before they the balloon put in, then when it comes out and again during the follow up period.

**6.3 What other support will be available?**

There will be a dietician available to give advice about healthy eating and to help plan balanced meals.

As an integral part of the study, an exercise science officer from Hallam University will be available to offer support and advice around lifestyle issues and will give you tailored advice around physical activity.

You will see them weekly for the first 9 months of the study.

There will be several phases in this programme.

**Life before the balloon-**4 weeks to prepare your child for the balloon going in

**Living with the balloon**-8 weeks focussing on the experience of your child

**Life after the balloon**-8 weeks to focus on education and behavioural support, diet and life style

**Life ahead**-8 weeks to prepare for life after the balloon has been removed, including physical activities and life style changes

**Relapse prevention**-Motivation to maintain the weight loss will be the focus of these 8 weeks.

We (the doctors/nurses at the hospital) will see your child again at 12 months, 18 and 24 months from the start of the study to find out how they are doing.

The physical activity sessions will include exercises, mini games with a fun element to them and last about an hour. They will be run at community facilities near your home or at Hallam University.

As previously explained, there will be 8 home visits by the exercise science officer monthly before the balloon goes in, while the balloon is in and for another month after that to help support the whole family through the programme.

6.4 **How much school will my child miss?**

We will try our very best to avoid your child missing school.

* The exercise and lifestyle management programme will be arranged in the late afternoons/evenings.
* There will be 3 days of tests over the 2 years which can be carried out during school holidays if you and your child would prefer.
* Your child will also need 1 day off when the balloon is put in and then a further day for taking it out. This can also be planned for a Friday or school holidays.
* We would like to see your child in the clinic every month to measure them when the balloon is in but this can be done after school.

**7.0 What will we have to do as parents and carers?**

We will need you to provide both physical and emotional support to your child during this study. It will involve significant changes in diet and lifestyle for the young person and family support will be crucial in both achieving and then maintaining the weight loss. You will need to bring your child in for the hospital visits and support sessions.

**8.0 What about travel costs?**

We will pay all the costs (taxi fare or parking if you come in your own car and mileage or bus/tram/ train fare up to a maximum of 40 pounds) for you to get to the hospital from your house for the tests before and after the balloon as well as for when the balloon is put in and taken out. You will need to provide us with the tickets/ invoices etc.

**9.0 What are the possible disadvantages and risks of taking part?**

Some discomfort with cramping, nausea , vomiting and diarrhoea for the first few days after the balloon goes in as the digestive system adjusts to the presence of the balloon is quite common (seen in 3 out of 4 people ). These side effects are temporary and normal.

It is important to follow instructions and drink plenty of fluids.

There could also be a feeling of heaviness in the abdomen or back pain which will all settle down over the next few days.

Sometimes the balloon can deflate early (hunger, weight gain and loss of feeling of fullness will be some of the signs) and usually it will pass right through. Very occasionally, they may need removing by operation.

More serious side effects include:

There is a small risk that the camera (changed from scope) could damage your child’s food pipe but this is very unlikely as the tube is flexible and the doctors doing the procedure are very experienced.

There is also a very small risk of having a serious reaction to the anaesthetic (1 in 20,000) but modern anaesthetic medicines are very safe and your child will be put to sleep by a children’s anaesthetist (someone who is specialised at putting children to sleep for operations).

About 1 in 10 people can get a sore throat but there are medicines to help you with this.

The main risk is blockage of the gut by the balloon (1.5 in a 1000). This is very rare and you will be told what to look out for. (Sickness or a bloated stomach for example). It is usually a problem in patients who have had previous gut operations but we have chosen your child because they have not had a gut operation before.

In a large adult study looking at more than 3000 patients, 2 patients died after a gut perforation but these were adults who had had previous gut operations. Considering, that children’s hearts and arteries are much healthier, we expect a much lower rate of problems and certainly the few studies done with young people did not show any adverse effects or problems with putting the balloon in or taking it out.

Other problems like ulcer (1 in 1000) and inflammation of the lining of the food pipe (oesophagitis, 2 in 1000) get better with medicines.

You will be given contact numbers to speak to a member of the research team if you are at all worried.

We do not know what effect losing a large amount of weight quickly has on growing bones. We therefore want to look at the thickness and strength of the bones before the balloon goes in and after it is removed. This means two types of scan - a special x-ray image called DEXA and a detailed type of X-ray called a peripheral CT scan. The scans take about 30 minutes and your child will be awake whilst they happen. They do not hurt but your child will have to lie still. The scans mean that your child will be exposed to some radiation. We are all exposed to a certain amount of radiation from the environment around us and this is called ‘background radiation’. This can be more when we do certain activities like take a flight or live in a certain area. The amount of radiation that your child will be exposed to during this study is equal to the background radiation they receive from the environment over 18 days or having their chest x rayed 6 times.

We plan to do the X-rays 3 times (before the balloon goes in, again after it comes out and then at follow up 18 months later).

**10.0 What are the possible benefits of taking part?**

The main advantage of taking part is the likely weight loss your child will experience, an average of approximately 3 stone in studies in adults. In other children, we have seen improvements in self confidence, increased physical activity and ability to make friends. Your child will also get individual advice and attention on lifestyle changes and exercise to help them to reach and then stay a healthy weight from a qualified exercise science officer (like having a personal trainer!). There will also be the chance to meet with other young people with similar worries and concerns.

**11.0 What will we do if we find a condition that you don’t know about during the study?**

Any problems/abnormalities found on blood tests or when examining your child will be discussed with you and your child by the research doctor who will then arrange for them to be seen by the appropriate consultant or their team.

There is a possibility that we may find problems like high blood pressure, early or pre-diabetes, abnormal liver tests and low vitamin levels. These conditions are all treatable and will in fact improve with weight loss that we hope to see with the use of the balloon.

**13.0 What happens when the research study stops?**

We will put together all the information we have got and analyse it to find out if using the balloon to bring about weight loss is safe, effective and acceptable to the young people and their families.

1. **Contact for further information**

If you would like any further information about this study you could contact:

*Name: Pooja Sachdev*

*Designation: Clinical Research Fellow*

*Hospital/Department: Sheffield Children’s Hospital*

[*Tel:*](Tel:0114) *07758312434*

**This completes Part 1 of the Information Sheet.**

**If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.**

**Part 2 - more detail – information you need to know if you still want to take part.**

**15.0 What if new information becomes available?**

Sometimes while doing the research study, new things are discovered and information can become available about the best way to treat severe overweight in young people or about the balloons we are using in this project.

If this happens, someone from the research team will tell you and your child about it and discuss with you whether you want your child to continue in the study. If you change your mind this will not affect any care your child receives whilst in hospital. If you decide to continue in the study you and your child will be asked to sign an updated form.

**16.0 What will happen if we don’t want to carry on with the research?**

If you want the balloon to be taken out before the six months is up, we will arrange for your child to come into hospital and have it taken out. We would still be interested in collecting data about your child –things like blood tests, scans, height and weight if you were willing to do so.

If you would like to withdraw completely from the study, that is also okay

Your child’s medical care will not be affected at all, so you do not have to worry.

***17.0 What if there is a problem?***

**Complaints**

If you have any cause to complain about any aspect of the way in which you or your child has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and do not change in any way because you have taken part in a research study. If you have any complaints or concerns please contact either the project co-ordinator:

Name: Pooja Sachdev

Designation: Clinical Research Fellow

Hospital/Department: Sheffield Children’s Hospital

Tel: 07758312434

Otherwise you can use the normal hospital complaints procedure and contact the following person:

Mrs Linda Towers

Patient Advice & Liaison Co-ordinator

Sheffield Children’s NHS Foundation Trust

Tel: 0114 271 7594

The overall responsibility for the study rests with the Director of Research and Development, Dr Jim Bonham

Telephone: 0114 2717404

Fax: 0114 27117417

Email: jim.bonham@sch.nhs.uk

**Harm**

If your child is harmed by taking part in this research project, there are no special compensation arrangements. If your child is harmed due to someone else's fault or negligence, then youmay have grounds for a legal action – but you may have to pay for it.

**18.0 Will taking part in this study be kept confidential?**

All information which is collected about your child during the course of the research will be kept strictly confidential. Any information about your child which leaves the hospital will have their name and address removed so that your child cannot be recognised from it. Once the study is complete all information will be kept in your child’s confidential notes.

Our procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

Blood test and bone scan results as well as questionnaires will be coded and pseudoanonymised and kept for a period of 5 years after the study finishes and then destroyed. Relevant medical information which could make a difference on your child’s future health information will continue to be kept in your child’s confidential medical notes.

The data will not be kept for use in further studies.

We will also ask for permission to inform your family GP that your child will be taking part in the study.

We will also ask for permission to look at your child’s school attendance records and results in national reference examinations if available. You do not have to give this permission.

Your child’s medical notes may also be looked at by other people within the hospital and the regulating bodies involved in the running and supervision of the study to check that it is being carried out correctly.

**19.0 What will happen to any samples my child gives?**

All blood and urine samples provided by your child related to the study will be anonymised and coded with a study number and stored in the Clinical Research Facility at the Children’s Hospital. However, the researchers will be able to identify the results of tests if any abnormalities are identified and you will be informed. These will be treated as they would have been if the child was not participating in the study-that is being in the study will not affect the medical care your child will receive.

No blood or tissue samples will be stored beyond the length of the study.

**20.0 Will any genetic tests be done?**

No.

**21.0 What will happen to the results of the research study?**

When the study has finished we will present our findings to other doctors, and we will put the results in medical literature and websites that doctors read. We would also like to put a brief summary on the hospital research website so that you will be able to read about our results too. This will be available at the end of the study, **in March 2014***,* on [www.sheffieldchildrenscrf.nhs.uk](http://www.sheffieldchildrenscrf.nhs.uk). The results will also be included as part of the chief investigator’s educational qualification. They will be anonymous, which means that your child will not be able to be identified from them.

**22.0 Who is organising and funding the research?**

The research is being organised by Sheffield Children’s NHS Foundation Trust and is being paid for by CLAHRC (Collaborations for leadership in Applied Health Research and Care for South Yorkshire)

**23.0 Who has planned / reviewed the study?**

Children’s doctors, nurses and trained psychologists, specialising in overweight and weight management in children have helped plan the study. It has also been looked at by independent experts to make sure that the study is scientific and safe.

Members of the public have also helped to develop this project. Two patients and three parents who have experience of balloons or weight loss surgery or are thinking about them have helped to design the project. They told us what is most important for young people-things like self confidence, friendships and school which affect their quality of life. They told us at what time intervals the questionnaires should be given out during the study. The involvement of this group will continue all through the project including designing these sheets and displaying the results of the study.

This study was given a favourable ethical opinion for conduct in the NHS by the Sheffield Research Ethics Committee. It has also been approved by the Research Department at this hospital.

**24.0 How can we find out more about research?**

The Clinical Research Facility at this hospital has Information **for families** section on its website [www.sheffieldchildrenscrf.nhs.uk](http://www.sheffieldchildrenscrf.nhs.uk) or you could contact the hospital Clinical Research Facility:

Mrs Wendy Swann

R&D Manager

Sheffield Children’s NHS Foundation Trust

Tel: 0114 226 7904

**If you and your child decide to take part in this study, you will be given this information sheet and signed consent and assent forms to keep.**

**Thank you for taking the time to read this information sheet.**



**Appendix 3b - PARTICIPANT INFORMATION SHEET FOR YOUNG PEOPLE**

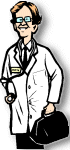
**Study title**

*The effectiveness and acceptability of stomach balloons as a treatment of severe adolescent obesity-BOB Study*

**Part 1 – to give you first thoughts about the project**

1. **Invitation paragraph**

We would like to invite you to be part of our research study. Please read this information carefully and talk to your mum, dad or carer about the study. Please ask us if there is anything that is not clear or if you want to know more. Take time to decide if you want to take part. It is up to you if you want to do this. If you don’t then that’s fine, you’ll be looked after at the hospital just the same.

1. **Why are we doing this research?**

We are doing this study to find out if a balloon placed in the stomach of severely overweight young people (ages between 13-16 years) for 6 months, along with diet and exercise can help them lose weight. We also want to know if the weight stays off for at least 18 months.

**2.1 What are the risks of being overweight?**

A small number of children and young people (about 3 in every 10,000) have weights around 90-150 kg (14-24 stone). Such young people can have health problems because of their weight while they are still young. They also have a greatly increased risk of developing diabetes and high blood pressure later in life.

Research suggests that worries about their weight can affect these children’s quality of life. Very obese children are more likely to suffer from low self esteem, depression and poor school attendance.

**2.2 What do we know about weight loss and balloons?**

Putting a balloon in the stomach (intragastric balloons or stomach balloons) to help people lose weight has been used for a long time. They work by reducing the size of the stomach so that the person feels full sooner and therefore eats less food. Research in adults has shown weight loss of about 3 stone/ 18 kg with them but because people tend to put on weight after the balloon is removed, permanent weight loss surgery is preferred in adults.

We think balloons may work better in young people because:

**a) They are safer** with much fewer complications than the weight loss surgery which is the other option severely overweight young people have.

This treatment is not planned for young people who are a little overweight - for them diet and lifestyle changes is the best thing.

**b) Children are more able to change their habits**

Balloons are a temporary way of promoting weight loss as they stay in for only 6 months. However once the balloon is removed we think young people are more likely to continue with new eating and exercise habits than adults, and so the weight loss is more likely to continue.

**c) There has been a small amount of research to say they work in young people**

A small number of research studies have shown the balloon does work in helping young people to lose weight. However, only a few studies have continued to measure weight loss once the balloon is removed. Many of these studies did not use a diet and exercise programme run by trained professionals either.

We want to find out how much weight young people lose with the stomach balloon and whether they continue to lose weight or put it back on again over the 18 months after the balloon is removed. We also want to look at how the weight lost helps young people in their day-to-day lives with school, physical activities and friends.

**3.0 What are we going to study?**

We want to study a number of different things:

a) How much weight is lost in the 6 months that the balloon is in the stomach?

b) Is this weight loss maintained for up to 18 months even after the balloon has been removed?

c) Does weight loss improve your quality of life?

d) What impact does the weight lost have on how you feel about your friendships, your school life as well as your physical fitness?

e) Is long-term health improved?

Does weight loss following the balloon help blood pressure, cholesterol levels, liver tests and the body’s ability to handle sugar?

f) Does losing a large amount of weight quickly affect the growing bones?

1. **Why have I been invited to take part?**

You have been invited to take part in this project because your doctor thought based on your measurements that you would be suitable for the study. We think the programme will be of benefit to you and your family, in helping to lose weight and in leading a healthier life style.

Some of the young people taking part in the study came forward themselves with their parents and carers after seeing some adverts and posters around the hospital and some of the others have had the study suggested to them by their consultant or their counsellor in a weight management programme.

1. **Do I have to take part?**

No! It is entirely up to you. If you do decide to take part:

- You will be asked to sign a form to say that you agree to take part (an assent form)

- You will be given this information sheet and a copy of your signed assent form to keep.

You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive whilst in hospital.

6.0 **What will happen to me if I take part?**

* There will be an initial meeting to make sure that the project is right for you and to answer any questions you may have and take consent from you and your parents.
* You will have a stomach balloon put in while you are asleep which takes about 20-30 minutes. This will stay in for 6 months and then removed again while you are asleep.
* The project will involve blood tests, urine tests and X-rays (changed from bone scans) before and after to look at the how weight loss affects your health and bones.
* We will also measure your weight, height and blood pressure regularly.
* We also want to find out how your weight affects your quality of life-things like self-confidence, your friendships, school and physical activity. We will do this by asking you to fill out some questionnaires.
* You will also attend a weekly support session where you will talk through different areas of your life, receive food and physical activity advice as well as participate in some physical activity. This will be at a sports centre near where you live or at Hallam University.
* The exercise science officer will also visit you at home, (while the balloon is in), to support you and your family
* **At 3 months (the half way stage of having the balloon in and at 6 months after the balloon is out), you and your family will take part in a discussion group to find out how you found the project. This gives you the chance to be honest with the research team about how you think the project is going and if you would change anything.**

A flow chart to explain how the study will work is included at the end of this information sheet.

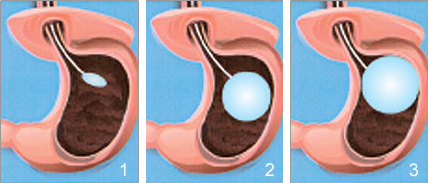
**6.1How will the balloons be put in and taken out?**

The balloons will be put in after you have been put to sleep by using a general anaesthetic. A children’s doctor who specialises in gut problems will put them in. The anaesthetic medicine will be given through a cannula (thin, plastic tube) in a vein in your arm. This area will already have been made numb using ‘magic cream’ or local anaesthetic. Your parents will be with you all the time that you are awake.

**The gut specialist will use a thin plastic tube with a camera at one end to put the balloon down your food pipe and this will take between 20-30 minutes. We do not have to cut you open. The balloon will be** **filled with salt** **water and left in for 6 months. The balloon will be removed in exactly the same way six months later. The balloons are made of a silicone material so they will not burst. You will usually be able to go home the same day once you are feeling better and have had something to drink. However, if you are being sick, we may keep** **you in hospital** **overnight.**

**You will need to take rest for 1 day when the balloon goes in and again after it comes out.**

**For the first few days after the balloon goes in, you will be on a liquid diet and asked to drink lots of water. After that, the dietician will recommend semi-solids and you will slowly go back to a normal healthy diet with some calorie restriction in place.**

****

**This is how the balloon looks when it is inside the stomach.**

**6.2 How will we measure the changes that take place?**

We will find out what changes have taken place by doing some tests before the balloon goes in and after it has come out .To find out how much weight you have lost, we will measure your height and weight.

To find out how your health has improved, we will measure your blood pressure, and also do tests to look at how your liver and kidneys are working. We will also measure your cholesterol levels and look at how healthy your bones are.

We will also do a test called Oral glucose tolerance test (OGTT for short) to find out how your body deals with sugar. A small hollow plastic tube (cannula) will be placed in a vein in the arm/hand and this will be bled back like a tap for blood tests. The back of the hand will be made numb by using an anaesthetic cream before the cannula is put in, so it should not hurt you.

It is important not to have anything to eat on the morning of the test though you can have tea as normal the evening before.

To find out how being overweight affects your life, we will ask you to fill 3 questionnaires about school life, P.E, your friendships etc. We will ask you to fill out these questionnaires before the balloon is put in, when it comes out and again when we see you to find out how you are getting on.

**6.3 What other support will be available?**

There will be a dietician available to give you advice about healthy eating and to help plan balanced meals.

As an integral part of the study, an exercise science officer from Hallam University will give you support and advice around lifestyle issues and physical activity. You will see them weekly for the first 9 months of the study.

The physical activity sessions will include exercises, mini games with a fun element to them and last about an hour. They will be run at community facilities near your home or at Hallam University.

**6.4 How much school will I miss?**

We will try our best to see that you miss school as little as possible.

The exercise and lifestyle management programme will be arranged in the late afternoons/evenings.

There will be 3 days of tests over the 2 years which can be done during school holidays after discussion with your parents and you.

You will need to have 1-2 days off school when the balloon is put in and again when it is taken out. This can be done on a Friday or again during school holidays.

We would like to see you every month for the 6 months when the balloon is in to make sure you are doing okay but we can do this after school.

**7.0 Is there anything else to be worried about if I take part?**

There can be some discomfort in your belly along with feeling sick and perhaps vomiting for the first few days after the balloon goes in as your body gets used to the balloon. Three out of four people experience this but it should settle soon. But it is important to follow what the doctor tells you regarding what you can eat and drink.

Sometimes the balloon can deflate early (if you start feeling hungry and not as full as before or start gaining weight we need to think about this) and usually they will pass right through your bowel and come out the other end. Very occasionally, the balloon may need removing by operation.

There is a very small risk that the camera could damage your food pipe but this is very rare as the tube is flexible and the doctors doing the procedure are very experienced. There is also a small risk of reacting to the anaesthetic but you will be put to sleep by a young person’s anaesthetist (someone who is specialised at putting children to sleep for operations).

The main risk is blockage of the gut by the balloon (1.5 in a 1000). This is very rare and you will be told what to look out for. (Things like sickness or a bloated stomach for example). It is usually a problem in patients who have had previous gut operations but we have chosen you because you have not had a gut operation before.

We also want to look at the thickness and strength of the bones before the balloon goes in and after it is removed to see how the weight loss affects growing bones.This means two types of scan - a special X-ray image called DEXA and a detailed type of X-ray like a CT scan. The scans take about 30 minutes and you will be awake whilst they happen. They do not hurt but you have to lie still. The scans mean that you will be exposed to some radiation. We are all exposed to a certain amount of radiation from the environment around us and this is called ‘background radiation’. This can be more when we do certain activities like take a flight or live in a certain area. The amount of radiation that you will be exposed to during this study is equal to the background radiation you receive over 18 days as part of your normal activity or having your chest x rayed 6 times. We plan to do the bone scans before the balloon goes in, again after it comes out and then at follow up 18 months later.

1. **What if you find something wrong with me on the tests that you do?**

If we find out something that we think is important on your blood tests, we will talk to you and your mum, dad or carer and ask you and them if you want to come back and get checked again at the hospital.

There is a possibility that we may sometimes find problems like high blood pressure, early or pre-diabetes, abnormal liver tests and low vitamin levels. These conditions can all be treated and will get better with the weight loss that we hope to see with the use of the balloon.

1. **Will the study help me?**

The study may help you. We are hoping that you will lose weight perhaps up to 3 stone when you take part in this study. This we hope will have a positive impact on all elements in your life. In other children, we have seen improvements in self-confidence, increased physical activity and ability to make friends. You will also get individual advice and attention on lifestyle changes and exercise to help you to reach and then stay a healthy weight from a qualified exercise science officer (it will be like having a personal trainer!). There will also be the chance to meet with other young people your age with similar worries and concerns.

1. **What happens when the research study stops?**

We will collect all the information together and decide if stomach balloons are useful in losing weight and improving the quality of life of young people with severe overweight problems.

1. **Contact for further information**

If you would like any further information about this study, you could contact:



Name: Pooja Sachdev

Designation: Clinical Research Fellow

Hospital/Department: Sheffield Children’s Hospital

[Tel:](Tel:0114) 07758312434

**Thank you for reading so far - if you are still interested, please go to Part 2:**

**Part 2 - more detail – information you need to know if you still want to take part.**

1. **What if new information comes along?**

Sometimes while doing the research study, new things are discovered and information can become available about the best way to treat severe overweight in young people or about the balloons we are using in this project.

If this happens, someone from the research team will tell you and your mum/dad or carer about it and discuss with you whether you want to continue in the study. If you change your mind this will not affect any care you receive whilst in hospital. If you decide to continue in the study, you and your parents will be asked to sign an updated form.

1. **What if I don’t want to do the research anymore?**

Just tell your mum, dad, carer, doctor or nurse at any time. They will not be cross with you. We will arrange for the balloon to be removed and you and your parents can decide if you want to carry on with the study. You will still have the same care whilst you are at hospital.

1. **What if there is a problem or something goes wrong?**

Tell us if there is a problem and we will try and sort it out straight away. You and your mum, dad or carer can either contact the project co-ordinator:

Name: Pooja Sachdev

Designation: Clinical Research Fellow

Hospital/Department: Sheffield Children’s Hospital

Tel: 07758312434

or the hospital complaints co-ordinator:

Mrs Linda Towers

Patient Advice & Liaison Co-ordinator

Sheffield Children’s NHS Foundation Trust

Tel: 0114 271 7594

1. **Will anyone else know I am doing this?**

The people in our research team will know you are taking part. The doctor looking after you while you are in hospital will also know.

If you and your parents agree, we will also tell your family doctor (GP) that you are doing the study.

Other people who work at the hospital or in organisations that monitor research studies may also look at your medical notes to check that the study is being carried out correctly.

All information that is collected about you during the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it, except for letters to your family doctor (GP). You will be given a number, which will be used instead.

Once the study is complete all the information, which is relevant to your medical care, will be kept in your own confidential notes and anything else will be destroyed.

Any data, photographs, questionnaires collected will be kept anonymised (which means we cannot find out who you are from it unless we have your special number) and kept for 5 years after the study is finished in case we need to go back and look at something.



1. **What will happen to any samples I give?**

All blood samples provided by you will be anonymised and coded with a study number and stored in the Clinical Research Facility at the Children’s Hospital. However, the researchers will be able to identify the results of tests if any problems come up on the test and you, your parents/carer will be informed, and the correct treatment started. .

We are not planning to use these samples in any other studies. We will not store any blood or tissue samples after the study is completed.

1. **What will happen to the results of the research study?**

When the study has finished, we will present our findings to other doctors, and we will put the results in medical journals and websites that doctors read. We would also like to put a summary on the hospital research website so that you will be able to read about our results too. This will be available at the end of the study, in March 2014*,* on [www.sheffieldchildrenscrf.nhs.uk](http://www.sheffieldchildrenscrf.nhs.uk). The results will also be included as part of the chief investigator’s educational qualification. They will be anonymous, which means that you will not be able to be identified from them.

**18.0 Who is organising and funding the research?**

The research is being organised by Sheffield Children’s NHS Foundation Trust and is being paid for by CLAHRC (Collaborations for leadership in Applied Health Research and Care for South Yorkshire)

1. **Who has checked the study?**

Before any research goes ahead, it must be checked by a Research Ethics Committee. This is a group of people who make sure that the research is OK to do. The Sheffield Research Ethics Committee has looked at this study. It has also been checked by the Research Department at this hospital.

1. **How can I find out more about research?**

The Clinical Research Facility at this hospital has Information **for families** section on its website [www.sheffieldchildrenscrf.nhs.uk](http://www.sheffieldchildrenscrf.nhs.uk) or you could contact the hospital Clinical Research Facility:

Mrs Wendy Swann

R&D Manager

Clinical Research Facility

Sheffield Children’s NHS Foundation Trust

Tel: 0114 226 7904

**Thank you for taking the time to read this – please ask any questions if you need to.**



**Appendix 4a - 16+ CONSENT FORM**



Patient study number:

**16+ CONSENT FORM**

**Title of project: A feasibility study of the acceptability and efficacy of intra-gastric balloons for the treatment of severe adolescent obesity and the metabolic and psychosocial effects of weight loss- BOB study or the Balloons in Obesity Study**

Names of researchers: Pooja Sachdev, Jerry Wales, Neil Wright

**Please initial box**

1. I confirm that I have read and understand the information sheet

dated 05.04.2012(version 4.0) for the above study and have had the

opportunity to ask questions.

1. I understand that my participation is voluntary and that I am free to

withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

1. I understand that relevant sections of any of my medical notes may be looked at by researchers and those involved in the running and supervision of the study from Sheffield Children’s NHS Foundation Trust or from regulatory authorities, where it is relevant to me taking part in research. I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of participation in this study.

5. I agree to take part in the above study.

6. I agree to my school attendance records being looked at by researchers

7. I agree to allow the researchers to look at my national reference exams results

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Name of Participant Date Signature

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Name of Person taking consent Date Signature

(if different from researcher)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Researcher Date Signature

1 copy for participant; 1 copy for researcher; 1 copy to be kept with hospital notes

Appendix 4b) **PARENT/LEGAL GUARDIAN CONSENT FORM**

Patient study number:

**PARENT/LEGAL GUARDIAN CONSENT FORM**

**Title of project: A feasibility study of the acceptability and efficacy of intra-gastric balloons for the treatment of severe adolescent obesity and the metabolic and psychosocial effects of weight loss- BOB study or the Balloons in Obesity Study**

Names of researchers: Pooja Sachdev, Jerry Wales, Neil Wright

**Please initial box**

1. I confirm that I have read and understand the information sheet

dated 05.04.2012(version 4.0) for the above study and have had the

opportunity to ask questions.

1. I understand that my child’s participation is voluntary and that I am free to

withdraw my child at any time, without giving any reason, without my child’s

medical care or legal rights being affected.

1. I understand that relevant sections of any of my child’s medical notes may be looked at by researchers and those involved in the running and supervision of the study from Sheffield Children’s NHS Foundation Trust or from regulatory authorities, where it is relevant to my child taking part in research. I give permission for these individuals to have access to my child’s records.

4. I agree to my child’s GP being informed of participation in this study.

5. I agree to my child taking part in the above study.

6. I agree to my child’s school attendance records being looked at by researchers

7. I agree to allow the researchers to look at my child’s national reference exams results

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Parent/Guardian Date Signature

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Person taking consent Date Signature

(if different from researcher)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Researcher Date Signature

1 copy for parent; 1 copy for researcher; 1 copy to be kept with hospital notes

**Appendix 4c - ASSENT FORM FOR CHILDREN & YOUNG PEOPLE**

**(To be completed by the child/young person and their parent/carer)**

**Title of project:** *The effectiveness and acceptability of stomach balloons as a treatment of severe adolescent obesity-BOB Study*

Participant study number:

Child (or if unable, parent on their behalf)/young person to circle all they agree with please:

Have you read (or had read to you) about this project? Yes / No

Has somebody else explained this project to you? Yes / No

Do you understand what this project is about? Yes / No

Have you asked all the questions you want? Yes / No

Have you had your questions answered in a way you understand? Yes / No

Do you understand it’s OK to stop taking part at any time? Yes / No

Are you happy to take part? Yes / No

**If any answers are ‘No’ or you don’t want to take part, don’t sign your name!**

**If you do want to take part, please write your name and today’s date**

Your name \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Your parent or carer must write their name here too if they are happy for you to do the project**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Parent/Carer Date Signature

**The person who explained this project to you needs to sign too:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Researcher Date Signature

Thank you for your help.

1 copy for participant; 1 copy for researcher; 1 copy to be kept with hospital notes



**Appendix 5 - Letter to GP’s of young people participating in the study**

From:

Children’s Clinical Research Facility,

D Floor, Stephenson Wing

Sheffield Children’s Hospital

Sheffield

<SCH ADDRESS>

To:

<GP ADDRESS>

<DATE>

Dear Practitioner,

**Re: A feasibility study of the acceptability and efficacy of intra-gastric balloons for the treatment of severe adolescent obesity and the metabolic and psychosocial effects of weight loss- also called the BOB study (Balloons in Obesity)**

<PATIENT DETAILS>

The above patient has agreed to participate in a research study to evaluate the impact of intragastric balloons over a 2 year period on weight loss, biomedical outcomes, quality of life, friendships and school.

The study is being supervised by Dr Neil Wright and Dr Jerry Wales, Consultant Paediatric Endocrinologists at Sheffield Children’s Hospital.

WHY ARE WE DOING THIS STUDY?

Childhood obesity in the UK is reaching epidemic proportions. Currently, approximately, 31% of children nationally are overweight and 17% are obese. Sheffield Children’s Hospital receives 100 referrals annually for children whose primary problem is obesity.

In a small number of these with significant obesity (13-16 year olds with weights between 90-150 kg with BMI> 3.5 SD for age and sex), (age range changed) there will be significant obesity related health problems whilst still young. These individuals also suffer major psychosocial effects as a consequence of their weight such as poor self esteem, depression and poor school attendance. Many drop out of school because of teasing & bullying and mental health problems with substantial long term costs to the individual, NHS and society.

NICE guidance suggests that bariatric surgery may be considered as a “first line” treatment strategy in adults with a BMI > 40 kg/m2. Although NICE guidance suggests that bariatric surgery may be appropriate for children in “exceptional circumstances” there is understandably a marked reluctance by paediatricians and commissioners to consider this.Treatments such as dietary moderation, behaviour management and pharmaceutical intervention have been found to be of very limited benefit in promoting weight loss in individuals with such large degrees of overweight.

We are therefore proposing a pilot study of intra-gastric balloons supported by a life style management programme to help severely obese adolescents lose weight and to follow these young people up 18 months later to see if the weight has stayed off.

Intra-gastric balloons (IGB) as a means to promote weight loss have been around for over 25 years . Fluid filled balloons are sited endoscopically and remain within the stomach for approximately 6 months. Its presence reduces the capacity of the stomach and enhances feelings of satiety. A recent systematic review ( 4877 patients, 30 studies of which 18 were prospective) showed a mean weight loss of 17.8 kg and a BMI change ranging from 4-9 kg/m2 Treatment related death rate was estimated at 0.07 % which compares favourably with the 1% quoted for bariatric surgery. Only 1 study assessed the effect on Quality of life and this demonstrated short term improvement. The impact of weight loss on improving comorbidities like hypertension and diabetes is also well documented.

Locally in Sheffield, our team has experience of developing, trialling & delivering interventions in obese children (Sheffield Obesity trial - SHOT). We also have experience of bariatric surgery in children (only UK centre) and experience with one child who had a balloon sited & lost 40 kg ( over 6 stone) in 6 months.

The intention is not to promote the technique for the routine treatment of childhood obesity but to investigate its utility in individuals with severe childhood obesity, at extremely high risk of health related and psychosocial problems.

It represents a safer and potentially more acceptable intervention (as it is temporary) for patients. In adults, surgery is preferred to balloon treatment in many cases because of

the risk of subsequent weight gain. We believe that children are more amenable to lifestyle changes than adults and that balloon therapy will kickstart these lifestyle changes which will be maintained and supported through a parallel behaviour management programme.

We intend to look at changes in weight, insulin resistance, lipid profile and BP before and after the balloon goes in. We also want to measure the incretin hormones secreted by the gut to investigate their role in glucose regulation and insulin resistance in obesity.

One concern about weight loss in childhood is as to whether it may reduce the accrual of bone mass into the skeleton. Adult studies have shown decreased total bone mass and density with both diet induced weight loss and bariatric surgery. We plan to look at bone density (DXA Scan), bone turnover markers and bone architecture (using HRpQCT as bone architecture correlates with fracture risk) to assess the impact of weight loss on the skeleton.

We also want to find out what effect the weight loss has on the young person’s Quality of life, friendships, self esteem and physical activity by completing 4 questionnaires at different time points.

To reinforce lifestyle changes, individuals will attend a support programme which includes behavioural therapy to set and maintain goals, exercise sessions run by an exercise science officer from Sheffield Hallam University.

**The key outcome is the extent of weight loss and the extent to which weight loss is maintained (BMI SDS at 6, 12 & 24 months).**

**Risks related to the intragastric balloon:**

Most patients will be able to go home the same day after the balloon has been put in. Some may need to stay in overnight if they are feeling sick or vomiting. For the first few days after the balloon goes in, the patient’s will have to be on a liquid diet, followed by a semi solid diet and then make a slow transition to a healthy diet with caloric restriction in place. Detailed instructions will be provided to them. They will need to be on a proton pump inhibitor for the 6 months that the balloon stays in.

A significant number will experience abdominal discomfort and some nausea and vomiting after the balloon goes in as the body gets used to having the balloon in place.

Sometimes the balloon can deflate early -hunger, weight gain and loss of feeling of satiety will be some of the signs they may present with. Usually, the deflated balloon will pass right through the gut into the colon and be passed out with stool. Very occasionally, they may need removing by operation. The participants will have detailed verbal and written instructions as well as a 24-hour contact number to ring while the balloon is in place.

The main worry is regarding the balloon causing intestinal obstruction (0.15%). This has however been a complication only in adult patients who have had previous bowel surgery and that is a specific exclusion criterion for our study. Patients will be warned of symptoms to look out for such as continuous vomiting, abdominal distension etc and the paediatric surgical team will be aware of the ongoing study.

Ulcers (0.1%) and oesophagitis (0.2 %) both of which can be treated conservatively are the other complications that may present while the balloon is in situ.

Your patient will be seen initially weekly (for 4 weeks) and then monthly while the balloon is in over the 6 month period.

As previously mentioned, this pilot study is targeted not at the average overweight child/young person but at the small number amongst those who are severely obese with weights ranging between 14-24 stone (90-150 kg) that are already at high risk of obesity related complications. For most of them, it is not a question of ‘if’ but ‘when’ for weight loss surgery.

We are unlikely to require access to their primary health care records.

Kindly do not hesitate to get in touch with us if you have any concerns or queries regarding this project.

Yours faithfully,

Pooja Sachdev

Clinical Research Fellow

C2

Academic Unit of Child Health

Stephenson Wing

Sheffield Children’s Hospital

Phone number: 07758312434

Email: pooja.sachdev@sch.nhs.uk

**Appendix 6 - Letter for surrounding units to help with recruitment**

Dear Doctor,

We would be extremely grateful for assistance in recruiting for the project outlined below.

**Subject: A feasibility study of the acceptability and efficacy of intra-gastric balloons for the treatment of severe adolescent obesity and the metabolic and psychosocial effects of weight loss-the BOB Study or the Balloons in Obesity Study.**

**Rationale and Background for the project**

A small number of young people have very severe obesity typically weighing between 90-150 kg. Such individuals suffer significant obesity related health problems as well as psychosocial effects as a consequence. As adults such individuals would be eligible for gastric band or bypass surgery in line with NICE guidance.Although the guidance does make provision for surgery in adolescents in exceptional circumstances there is reluctance amongst paediatricians to consider this. Weight & behaviour management programmes and pharmaceutical treatment for obesity are of limited benefit in some individuals.

We are proposing a feasibility study of intragastric balloons, (supported by a lifestyle program), to help severely obese adolescents (13-16 years) lose weight. The balloon is placed in the stomach endoscopically under anaesthetic and inflated with saline - it can be left for 6 months. The rationale for proposing a trial is that in adults balloons have been shown to promote a change in BMI of 4.0 - 9.0 kg/m2  and a mean weight loss of 17.8 kg. In adults because of concerns that individuals will subsequently regain weight, surgery is often preferred. However, in adolescents balloons may provide a more acceptable & cost-effective option than surgery - balloons are temporary rather than permanent. The risk of a serious complication is much lower at 0.07% compared to bariatric surgery (mortality approx 0.5-1%) Young peopleare more amenable to lifestyle change and by using balloons to “kickstart” weight loss, supported by a lifestyle management programme, we mayprovide a platform for longer term improvement in their weight.

We plan to look over a 2 year period at the impact both on children’s health (risk of diabetes, high blood pressure etc), but also importantly at depression, friendships, schooling etc which are more important from a young person’s perspective.

Locally we have experience of developing, trialling & delivering interventions in obese children. (Sheffield Obesity Trial. Exercise Therapy as a Treatment for Psychopathologic Conditions in Obese and Morbidly Obese Adolescents: A Randomized, Controlled Trial. *Pediatrics* 2006).

We also have experience of bariatric surgery in young people and experience with one teenager who had a balloon sited & lost 40 kg in 6 months.

**The key inclusion and exclusion criteria are listed below.**

Key Inclusion criteria:-

* BMI> 3.5 SD roughly equivalent to adult BMI of 40 kg/m2.
* To have attained or nearly attained adult stature and stage 4 pubertal development (age group between 13-16 years).
* Failed to attain a healthy weight with organized attempts at conventional weight management.
* Agree to avoid pregnancy for at least one year postoperatively (if sexually active).
* Are capable of and willing to adhere to nutritional guidelines postoperatively.
* Are willing to participate in weekly support programme
* Able to provide informed assent

Exclusion criteria (increased risk of adverse event in adult populations):-

* Previous gastric surgery or history of intestinal obstruction.
* History of inflammatory disease of the gastrointestinal tract such as oesophagitis, gastric or duodenal ulcers, or congenital anomalies such as atresias or stenosis.
* Hiatus hernia>5 cm.
* Significant psychological disorder
* Pregnancy

The procedure is expected to run as a day case and the attendant risks/precautions will be explained to patient/carer and made clear in the participant information sheets during the consent process.

We would be grateful if you could identify any patients who meet the eligibility criteria and discuss the project with them to see if they are interested and willing to be approached by the research team. If so, I would be grateful if you could drop me a quick line with their contact details.

Kindly do not hesitate to get in touch with me if you require any further information.

I am also enclosing a letter to be sent to parents/carers of your patients that you could send out on your behalf. I would be grateful if your contact details could be added on to this letter.

My contact details are included below:

Many thanks and best wishes

Dr Pooja Sachdev

Clinical Research Fellow

C2, Academic Unit of Child Health

Stephenson Wing

Sheffield Children’s Hospital

Damer Street

Sheffield

S10 2TH

Email :[Pooja.sachdev@sch.nhs.uk](mailto:Pooja.sachdev@sch.nhs.uk)

Phone: 07758312434

Chief Investigator: Dr Neil Wright, Consultant Paediatric Endocrinologist, Sheffield Children’s Hospital



**Appendix 7 - Letter for A&E/Children’s Hospital Access**

Dear Team,

This patient is taking part in a research study at Sheffield Children’s Hospital looking at the efficacy of intra-gastric balloons in helping severely obese young people to lose weight. The intra-gastric balloon is placed in the stomach endoscopically and stays in for 6 months. The Sheffield Research Ethics Committee has approved the study. Sheffield Children’s Hospital are the sponsors for the study and full R&D approval is in place.

Known side effects after balloon placement include nausea, vomiting, diarrhoea and stomach cramps. The patients are on regular anti-emetics and pain relief for the first few days. More serious problems include deflation of the balloon causing obstruction, perforation and peritonitis that would require surgery for balloon removal. The surgery and anaesthetic department here at SCH is aware of the project and will provide support in the event of an emergency.

The project is aimed at young people aged 13-16 years. Some of the young people in the study are now approaching 17 years. We would be grateful that they continue to be assessed here at the Children’s hospital for complaints pertaining to the balloon till the balloon is in situ. The medical team here at the Children’s Hospital will assess the young people older than 16 years of age in the first instance. The project will run through till December 2013.

Kindly get in touch with

Dr Neil Wright (0114 2717118) or

Dr Mike Thomson

(0114 2717673) or

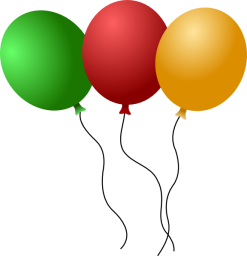
Dr Pooja Sachdev (07758312434) if there are any queries regarding this.

Best wishes and many thanks for your help.

Dr Pooja Sachdev

Dr Neil Wright

**Appendix 8 - BOB Study**

(Balloons in Obesity Study)

We are doing a study in children and young people (13-16 years) who are severely overweight. (>14 stone or 90 kg)

Every year, we see about 100 children and young people at Sheffield Children’s Hospital who are severely overweight. Diet and exercise have not been helpful for these young people. Stomach balloons are useful in helping adults to lose weight with an average weight loss of almost 3 stone seen in 6 months.

We want to find out how effective intragastric balloons together with diet and exercise are in bringing about weight loss in young people/children with severe overweight.

What will happen to me if I want to take part?

* There will be an initial meeting to make sure that the project is right for you and to answer any questions you may have.
* You will have a stomach balloon put in while you are asleep which takes about 20-30 minutes. This will stay in for 6 months and then be removed again while you are asleep.
* The project will involve blood and urine tests and x-rays before and after to look at the how weight loss affects your health and bones.
* We will also measure your weight, height and blood pressure regularly.
* We also want to find out how your weight affects your quality of life-things like self confidence, your friendships, school and physical activity. We will do this by asking you to fill out some questionnaires.
* You will also attend a weekly support session organised by the exercise and science officer from Sheffield Hallam University where you can talk through different areas of your life, receive food and physical activity advice as well as participate in some physical activity. This will be at a sports centre near where you live or at Sheffield Hallam University.

We will reimburse all travel expenses incurred up to an upper limit of 40 pounds per visit. If you would like more information, or wish to take part, please call 07758312434 or email [pooja.sachdev@sch.nhs.uk](mailto:pooja.sachdev@sch.nhs.uk)

Balloons in Obesity (BOB) Study

Advertisement

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05/04/2012

**Appendix 9a - Self reported pubertal staging in boys**

Subject number:-

FIRST look at the penis and scrotum (ONLY) in the picture. Please put a tick in the box that looks most like you now: -

SECOND look at the pubic hair (ONLY) in the picture. Please put a tick in the box that looks most like you now: -

|  |  |  |
| --- | --- | --- |
| 1. Scrotum and penis same size as when you were younger | 1. The scrotum has lowered a bit and the penis is a little larger | 1. The penis is longer and the scrotum is larger |
| 1. No hairs | 1. Very little hair | 1. Quite a lot of hair |
|  |  |  |

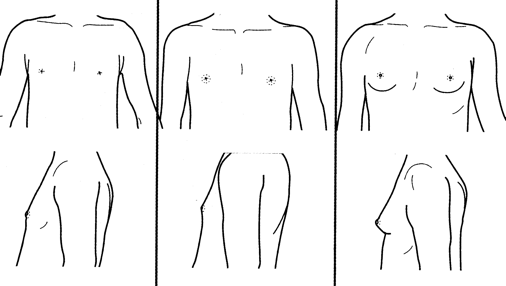
|  |  |
| --- | --- |
| 1. The penis is longer and wider and the scrotum darker and bigger than before | 1. The penis and scrotum are the same size and shape as an adult. |
| 1. The hair has not spread over the thighs | 1. The hair has spread on to the thighs |
|  |  |

**Appendix 9b - Self reported pubertal assessment for Girls**

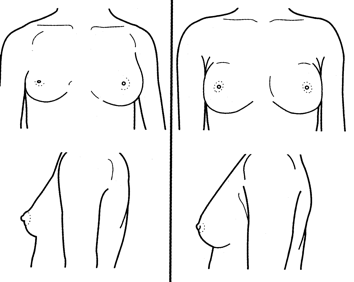
(Breasts)

Subject number

Look at the breasts and put a tick in the box that looks most like you now: -



|  |  |  |
| --- | --- | --- |
| Your breasts  are flat. | The breasts form small mounds. | The breasts form larger mounds than in 2. |



|  |  |
| --- | --- |
| The nipple and the surrounding part (the areola) make up a mound that sticks up above the breast. | Only the nipple sticks out beyond the breast. |

Girls (Pubic Hair)

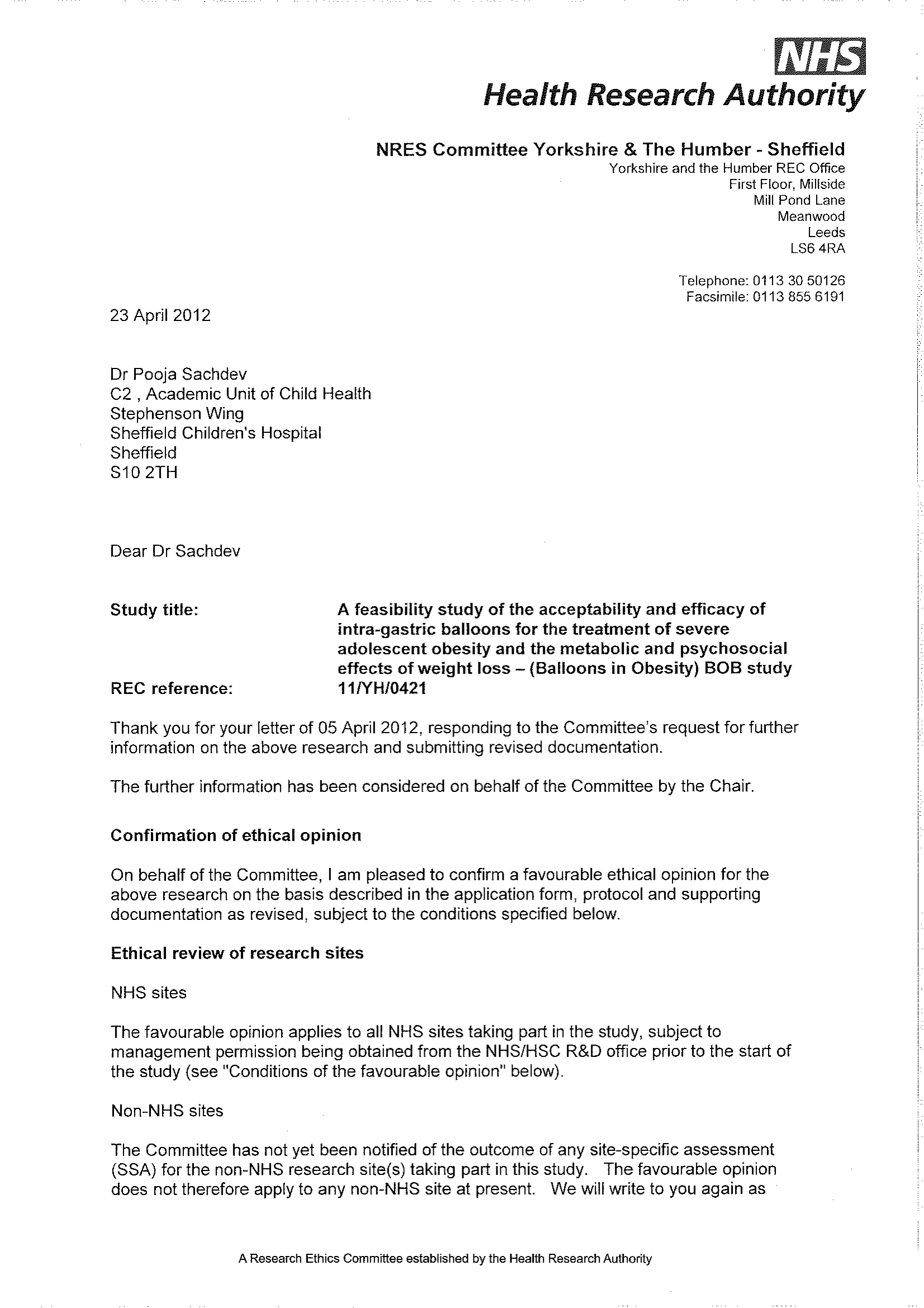
Subject number: -

Look at the pubic hair (ONLY) in the picture. Please put a tick in the box that looks most like you now: -

|  |  |  |
| --- | --- | --- |
| No hairs | Very little hair | Quite a lot of hair |
|  |  |  |

|  |  |
| --- | --- |
| The hair has not spread over the thighs. | The hair has spread on to the thighs. |
|  |  |

**Appendix 10 - Ethical approval**



**Appendix 11 - a-e Validated Questionnaires in the public domain**

**Appendix 12 - a-c Publications from the BOB Project**

**Appendix 13 - a-b Correlations between bone markers, adipokines and body composition and bone microarchitecture and strength**

**../Appendices%20for%20PhD/Appendix%2013a-Correlations%201-2%20and%202-3.pdf**

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| --- |
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