The BOW Study (Bone in Weight Loss): The effect of profound weight loss following intragastric balloon placement on skeletal integrity in severely obese adolescents.

Background:

The effect of profound weight loss following obesity surgery on cortical and trabecular bone structure and strength in adolescents has not been studied. A paradox exists in the way fat affects bone in children and adults. Obesity appears to protect against osteoporotic fracture in adults and dietary or surgery induced weight loss leads to decreased bone mass. In contrast bone mass relative to body size is reduced in obese children and obese children are at greater risk of fracture.

Twenty six percent of adult bone mass is achieved during adolescence through peak bone mass accrual and this predicts later osteoporotic risk. Bariatric surgery at this time may therefore profoundly reduce bone mass accrual. However, paradoxically it could improve the negative effect of obesity on bone, with weight loss leading to increased bone mass relative to body size and reduce the risk of fracture.

We conducted a study on the metabolic consequences of intra-gastric balloons (IGB) surgery supported by a lifestyle and exercise intervention programme as a less invasive and hazardous method (compared with bariatric surgery) to help severely obese adolescents lose weight. We also examined the impact of rapid and significant weight loss following intragastric balloon surgery on cortical and trabecular bone microstructure, integrity and strength in obese adolescents.

This was funded by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) and the BSPED (British Society of Paediatric Endocrinology and Diabetes).

Sheffield has one of only three clinical Xtreme CT scanners in the country capable of the in-vivo 3D study of cortical and trabecular structure to a resolution of 80 micrometres using High Resolution Peripheral Quantitative Computed Tomography (HRpQCT) (figure 1&2).

Measurements included cortical volume, area and porosity, trabecular number, density and volume We also have expertise in the biomechanical analysis of bone strength using microfinite element (microFE) analysis which co-relates to fracture risk.

With an increase in surgical intervention to treat severe obesity in adolescents, it is vital that the effects of rapid and profound weight loss on physiological adolescent development are clearly understood. This will direct therapies to

support optimum bone mass accrual during rapid weight loss to prevent fracture and early onset osteoporosis.

Figure 1: HRpQCT of the tibia

Figure 2: HRpQCT of the radius

Preliminary results:

. 12 patients (5 boys) were recruited to a pilot study looking at the feasibilty and effectiveness of intragastric balloons in severe adolescent obesity and the metabolic consequences of rapid and profound weight loss including the impact on skeletal health.

. Mean weight at baseline was 138.5 kg (SD ±23.9), BMI 46.4 kg/m^2 (SD ±5.6) and BMI SDS +4.0 (SD ±0.3). Anthropometric and metabolic assessments were carried out at baseline, at balloon removal at 6 months and then at 2 years (18 years post balloon removal).

. Our patients also underwent serial radial and tibial HRpQCT analysis over two years to define skeletal microstructure and strength in relation to changes in body proportions and percentage fat mass measured by DXA.

. The balloon was well tolerated with no significant complications and no early removals.

Average weight loss at 6 months at balloon removal was 7.0 kg with reduction in BMI of -2.53 kg/m2 and BMI SDS reduction of 0.2 SD. This represented a mean loss of 5% of initial body weight. At 12 months (6 months post balloon removal) mean weight was 138.4 kg (±21.7). All patients except 2 lost weight in the 6 months the balloon was in situ. However, weight loss was sustained in

only 2 participants at 24 months.

Results showed clinically relevant improvements in blood pressure, insulin: glucose metabolism, liver function and sleep apnoea at 6 months. Changes were not sustained at 2 years though some parameters (Diastolic BP, HBA1c, insulin AUC) demonstrated longer-term improvement despite weight regain. Despite weight loss, bone mass accrual as assessed by DXA showed age appropriate increases.

At the tibia, consistent gains were seen from baseline to 2 years in cortical area and cortical thickness while gains were only seen in cortical and trabecular bone mineral density (BMD) at the radius at 6 months. Over 2 years' bone stiffness and ultimate failure load at the radius and tibia increased.

There was no change in fasting ghrelin values, leptin and adiponectin.
There was a significant increase in fasting Glucagon like peptide-1 (GLP-1) over the 24 months and the area under the curve (AUC) for GLP-1 also improved at 24 months despite weight regain suggesting improved incretin effect.
We are still in the process of analysing the osteokine and bone turnover marker data and corelating this to the changes seen in incretins and skeletal micro-architecture.
This project has resulted in the following presentations and publications so far.

Oral Presentations

BSPED 2013 "*A feasibility study of intra-gastric balloons (supported by a lifestyle programme) for the treatment of severe adolescent obesity - the (BOB) Study"*. Oral presentation.

BSPED 2015 *"Impact of intra-gastric balloon bariatric intervention on skeletal microstructure and strength in severely obese adolescents - a longitudinal study".* Oral presentation.

BSPED 2016 "*Biomedical outcomes of weight loss associated with intragastric balloon therapy supported by a life style programme in severe adolescent obesity"*. Oral presentation.

ESPE 2015 *A Feasibility Study of Intra-Gastric Balloons (Supported By a Lifestyle Programme) for the Treatment of Severe Adolescent Obesity: 2 year follow up data. (Poster and oral)*

ESPE 2016 '*Impact of intra-gastric balloon bariatric intervention on skeletal microstructure and strength in severely obese adolescents at 6 months and 2 years - a longitudinal study'*. Oral presentation.

Papers:

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

2) Sachdev P, Reece LJ, Thomson M, Natarajan A, Copeland RJ, Wales JK, Wright NP. Intra-gastric balloon as an adjunct to lifestyle support in severely obese adolescents; impact on biomedical outcomes and skeletal health. doi:10.1038/ijo.2017.215

Benefit to applicant

I am now an NHS Consultant at Nottingham University Hospitals. I am working alongside on my PhD and planning to finish writing up in the next 12 months. This project has provided me with the opportunity to collaborate with well-established researchers in the Academic Unit of Child Health at Sheffield as well as at the Mellanby Bone Centre which has an international reputation in basic, translational and clinical bone research. I have had the opportunity to further my interest in this area of clinical endocrinology and develop a profile in endocrine research to further both my clinical and academic career. I plan to continue develop expertise in the management of severe obesity and type 2 diabetes in adolescence.

Benefit to the department/institution:

The endocrinology department at Sheffield Children's Hospital has an internationally renowned profile in paediatric bone metabolism including osteogenesis imperfecta. They have previously shown that obese children have a lower bone mass relative to body size and that key osteoclastogenic regulators are altered in relation to leptin in obese children resulting in an increase in bone resorption. We have also recently demonstrated that GLP2

may result in a direct increase in osteoclastic bone resorption by direct cell interaction. This project adds to our work on in-vivo fat bone interactions as part of our extensive programme in paediatric and young adult bone research including the development of in-vivo bone imaging in children.

Benefit to endocrine research

The rise in severe obesity (BMI>40 kg/$m^{2,}$) has led to increasing numbers of adolescents undergoing bariatric procedures with acutely significant weight loss. Diet and surgery induced weight loss in adults' results in decreased bone density and mass.
However, the skeletal response to weight loss in children may differ. One-quarter of bone mass in adulthood is achieved during adolescence and adolescent peak bone mass accrual is a major determinant of osteoporotic risk. Obese adolescents also have an increased fracture risk on a background of increased fracture risk in adolescence. Weight loss (sibutramine and diet-induced) leads to a decrease in appendicular bone mass but a paradoxical increase in spinal bone mass in children suggesting that the effect of weight loss on the growing skeleton may be region specific. A recent study in 61 adolescents who had Roux-en-Y Gastric Bypass (RYGB) showed significant bone loss (7.4 %) with decrease in both bone mineral content as well as density - though longer term predicted bone density was appropriate for age 2 years after the surgery.
Importantly, change in bone density and micro architecture must also relate to a change in bone strength and fracture risk. No study to date has used HRpQCT to determine the effects of bariatric surgery on cortical and trabecular bone structure and strength and there is no data to delineate the hormonal mechanisms that may underpin skeletal changes in adolescents during profound weight loss.
We have shown so far that in the short term, an IGB placement offers significant reduction in BMI SDS. There is some improvement in metabolic parameters and unlike other bariatric procedures, bone accrual during adolescence continued at a time when bone mass accrual is critical. Work on analysing the bone turnover markers, osteokines and their correlation with incretins and skeletal micro-architecture is on going.