



The Effect of Bariatric Surgery on Bone Health

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Authors' contributions

This work was carried out in collaboration between all authors. Author JM performed the literature search and wrote the article itself. Author IMC edited the first draft. Author KS formulated the review idea and edited the final draft.

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Review Article

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ABSTRACT

The prevalence of obesity, with its associated co-morbidities, is on the rise, and bariatric surgery is proving to be an effective means of allowing sustained weight loss as compared to alternative strategies. Follow up data is starting to accumulate showing evidence of the impact on bone metabolism, with associated clinical implications, including pathological fracture at a relatively young age. Furthermore this effect is seen to be different with regards to what type of procedure is performed. This review provides a summary on this topic, including an overview of the background science of bone metabolism and relates this to the nutritional sequelae of bariatric surgery. Follow up data on each procedure is reviewed, and recommended management and monitoring strategies discussed.

Keywords: Obesity; bariatric surgery; bone health; metabolic bone disease.

1. INTRODUCTION

Obesity is linked to many co-morbidities, including type 2 diabetes mellitus, cardiovascular disease, certain cancers and respiratory disease

[1]. Severe and morbid obesity (BMI between 35 and 39.9 kg/m² and ≥40 kg/m² respectively) sharply reduces life expectancy, especially in young adults [2].

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Bariatric surgery results in a higher degree of sustained weight loss, with reduced weight related co-morbidity and mortality, compared with conventional diet and weight loss strategies [3]. The aims of the anatomical and functional changes in the proximal gastrointestinal tract during bariatric surgery are to lead to impaired calorie digestion and absorption at more distal segments [1]. Consequent alterations in micro-nutrient absorption may lead to undesired metabolic side-effects. Surgery for weight-loss is becoming increasingly common; in 2012/13 over 8000 procedures were performed on the NHS [4]. Consequently the cohort of patients at risk of long-term metabolic side-effects of bariatric surgery is growing all the time.

Evidence of numerous metabolic changes after bariatric surgery is accumulating and data on associated clinical implications are becoming available. These include an impact on bone metabolism, leading to metabolic bone disease, with consequences such as pathological bone fracture. This review aims to summarize the basic science of bone metabolism, the background science underpinning metabolic bone disease and relate this to the nutritional sequelae of bariatric surgery. Recommended monitoring and management strategies from professional organisations will then be presented to inform the best practice.

2. NORMAL BONE HEALTH

Normal bone homeostasis is maintained by a complex interplay of dietary, hormonal and lifestyle factors. As bone is constantly turning over disruption of the factors outlined below will result in metabolic bone disease.

2.1 Calcium

The homeostasis of calcium levels is maintained by a combination of gut absorption, bone resorption and renal reabsorption [5]. Around 80% of calcium gut absorption occurs in the duodenum and proximal jejunum via a vitamin D dependent process [6]. The remainder is absorbed by passive paracellular processes in the remainder of the small intestine and colon [7].

Low serum levels of calcium stimulate release of parathyroid hormone (PTH). This stimulates increased osteoclast activity, increased bone resorption and release of calcium into the

circulation together with production of calcitriol [6-9].

2.2 Vitamin D

In addition to the roles outlined above vitamin D acts to maintain calcium homeostasis by modulating osteoblast activity and bone mineralisation [10]. Low vitamin D levels can result in secondary hyperparathyroidism, hypocalcaemia, osteomalacia and osteopenia.

Vitamin D absorption is bile salt dependant and occurs in the proximal and mid small bowel [8]. Vitamin D is also synthesised by melanocytes in response to ultraviolet-B exposure. Passive sun exposure is often inadequate to achieve required serum levels. A recent large cross-sectional survey of adolescents in Europe has shown deficiency in 81% of those tested. Vitamin D is stored in adipose tissue, and it is thought to be released into the circulation over time with weight loss; however it has been shown that circulating levels do not increase significantly following bariatric surgery, indicating a severe form of malabsorption [11].

2.3 Magnesium

Magnesium affects bone remodelling and strength and has a positive association with hip bone mineral density (BMD) [5]. It also plays an important role in calcium and bone metabolism [5]. Whilst acute hypomagnesaemia stimulates PTH secretion, chronic depletion leads to impaired PTH secretion (a magnesium-mediated process), with a resultant decrease in calcium and vitamin D levels [12]. Magnesium is absorbed in the distal small intestine. Surgical bypass of portions of the ileum result in deficiency via reduced absorption and chelation of available magnesium by unabsorbed fatty acids [13].

2.4 Vitamin B12

Vitamin B12 (cobalamin) deficiency may be a risk factor for osteoporosis and is associated with an increased risk of fracture [14]. Malabsorption is common when more than 60 to 100 cm of terminal ileum is bypassed [13]. Although the mechanism for this was initially believed to be decreased intrinsic factor production, it is actually due to decreased gastric acidity and poor release of cobalamin from dietary protein [15].

3. METABOLIC BONE DISEASE

3.1 Background

Metabolic bone disease incorporates a host of conditions including osteoporosis (“brittle” bone disease), osteomalacia (“soft” bone disease) and secondary/tertiary hyperparathyroidism, multiple myeloma and Paget’s disease. Osteoporosis is the most common metabolic bone disease, characterised by enhanced bone fragility due to a reduction in bone quantity and quality [16]. Osteomalacia is characterised by fragility due to reduced bone mineralisation, and is the result of vitamin D deficiency (with or without calcium deficiency). Secondary hyperparathyroidism, which occurs secondary to hypocalcaemia and low vitamin D levels, also contributes to osteoporosis and osteomalacia [17].

3.2 Aetiology of Osteoporosis

Osteoporosis has many inter-related risk factors with obesity. Risk factors for osteoporosis include increased age, postmenopausal status and type 1 diabetes mellitus. Lifestyle factors also affect risk such as smoking, high alcohol consumption, type 2 diabetes, obesity and a sedentary lifestyle. [5].

Weight loss is an independent risk factor for osteoporosis as demonstrated by the Framingham Osteoporosis Study (albeit this study was on an elderly population looking at longitudinal bone loss). Vitamin D levels were not found to impact BMD in this study although vitamin D deficiency is a common co-factor for all diseases of bone metabolism and is linked to obesity [18,19]. In men and post-menopausal women the protective effects of oestrogen (inhibits bone resorption) are reduced as decreased adipose tissue reduces the peripheral conversion of circulating androgens to oestrogens [20].

4. OBESITY AND BONE HEALTH

4.1 Bone-Adipose Axis

Adipocytes have an active role in calcium homeostasis, and there is evidence that adipose tissue and bone regulate each other in a complex feedback loop [21]. Adipokines, including leptin, adiponectin, tumour necrosis factor- α (TNF α) and interleukin-6 (IL-6), are released from adipose tissue. They have been shown to

influence bone deposition and resorption [22]. Adiponectin has a negative effect on bone formation via an indirect induction of osteoclast formation and osteoprotegerin mediated inhibition of osteoblast function [23].

Bone-derived factors (osteokines), such as osteoprotegerin, osteopontin (OPN), osteocalcin, and osteonectin are secreted from osteoclasts and osteoblasts, and exert endocrine regulation on glucose homeostasis and body weight [21]. Factors such as OPN have an active role in bone turnover by acting as an attachment for osteoclasts, thus activating the resorption cascade [24]. OPN is also involved in a variety of pathophysiological processes, including immunity, inflammation, neoplastic transformation and cardiovascular function [21].

Oestrogen has a protective effect on BMD. Increased bone density associated with obesity was thought to be due to simple mechanical loading [25]. However increased bone density is also observed in bones associated with non-weight bearing joints in obese individuals [26]. This effect is mediated by oestrogen; cessation of oestrogen production promotes high bone turnover and decrease in BMD of 4% per year [27,28]. Adipose tissue is the main site for oestrogen production in post-menopausal women and men via the action of aromatases which convert circulating androgens to oestrogen [29]. Post-menopausal status has a pronounced effect on bone metabolism and any effects related to surgery for weight loss are likely to be exacerbated in this group [20].

Obese individuals tend to have lower circulating levels of vitamin D. This is because it is primarily stored in adipose tissue; with higher levels of adipose tissue proportionally less vitamin D is available to the circulation [30,31].

There is still limited understanding regarding the precise interplay between adipose tissue and the skeleton and this field will provide extensive opportunity for further research into the pathways involved.

4.2 Pre-operative Nutritional Status

Obese individuals already have an increased risk for metabolic bone disease due to a combination of chronic vitamin D deficiency, reduced calcium intake and secondary hyperparathyroidism [5].

Micro-nutrient deficiency is often seen in the obese individuals, despite excessive calorie intake. In patients awaiting bariatric surgery, 60% are vitamin D deficient (25OH-vitaminD <50 nmol/l) and 90% have insufficiency (25OH-vitaminD <75 nmol/L) [32]. Low levels of vitamin D in the obese population are partly attributed to reduced sunlight exposure and reduced intestinal absorption [31].

4.3 Weight loss and BMD

It is generally observed that a 10% voluntary weight loss results in a 1-2% loss of bone mass at all sites [5]. However more rapid weight loss results in a more significant degree of bone loss, due to activation of the calcium-parathyroid hormone axis [33]. This effect on bone loss is observed even when vitamin D and PTH levels are normal [34]. One study looking at weight loss secondary to lifestyle intervention observed a decrease in hip BMD nearly three times greater in women in the highest quartile for weight loss [35]. In general it appears that the effect on BMD is proportional to degree of weight loss [11]; however it remains unclear whether the extent of BMD change is proportional to weight loss, particularly in the postmenopausal setting [36].

The modality used to achieve weight loss also seems to impact on whether BMD is affected. Whilst caloric restriction-induced weight loss has been observed to be a risk factor for rapid bone loss, physical activity-induced weight loss preserves BMD [37].

5. OVERVIEW OF BARIATRIC SURGERY

Bariatric surgery is typically classed as restrictive, malabsorptive, or a hybrid procedure. Restrictive simply reduce food and calorie intake to drive weight loss. Malabsorptive procedures decrease the absorptive surface available in the intestine by bypassing segments reducing the amount of calories the body is able to absorb from food. Examples of the different types of procedures are shown in Table 1.

In general the more malabsorptive a procedure, the more weight loss is achieved. A meta-analysis revealed percentage excess body weight lost was 46% for gastric banding and 60% for RYGB [38]. In the UK, RYGB is the most commonly performed bariatric procedure, with LAGB being the most common restrictive procedure.

5.1 Roux-En-Y Gastric Bypass

A small stomach pouch is created which is then anastomosed to the jejunum, thus restricting food intake, whilst bypassing the distal stomach, duodenum and jejunum (Fig. 4).

The metabolic effects of this procedure are similar to subtotal gastrectomy. Long-term postoperative nutritional deficiencies are common, particularly in relation to iron, vitamin B12 and folate [39]. As the duodenum is the primary location for calcium absorption, bypass induces calcium malabsorption in the region of 24-36% (although this may be recovered with supplementation) [40] and a 29% increase in PTH levels [41]. A reduction in the absorption of fat soluble vitamins, including vitamin D, is seen due to the reduced mixing with bile salts [42]. The length of afferent limb impacts the extent of malabsorption, with an increased degree of secondary parathyroidism and vitamin D deficiency as afferent limb increases [43].

The effect on decrease in BMD with weight loss seems to be bone-site specific [11]. The hip/femoral neck and lumbar spine seem to be most commonly affected, with little evidence of an effect on other sites such as the radius, suggesting the level of mechanical stress is related to the degree of BMD loss. Within one year of RYGB, Johnson et al. [44] found total hip BMD decreased by 9.3% and lumbar spine BMD decreased by 4.5%, with no further decline after the second year. This suggests that decrease in BMD mirror weight loss with largest decreases initially, plateauing after one year. Other surrogate markers of bone loss show marked changes after RYGB. Urinary crosslaps (associated with bone resorption) increase 288% and osteocalcin (associated with bone formation) increases 53% [45].

Premenopausal status appears to mitigate the impact on BMD, with one small observational study finding no decrease in BMD in premenopausal women, whilst postmenopausal women showed decreased BMD [46].

Another interesting consequence that ileal bypass evokes is increased colonic resorption of dietary oxalate, especially in the distal colon [47]. This is due to fat malabsorption, resulting in the unavailability of free calcium to bind to oxalate in the gut, as well as unabsorbed bile salt-induced increases in colonic permeability to small

Table 1. Overview of bariatric procedures

Restrictive	Malabsorptive	Malabsorptive with restriction
Laparoscopic Adjustable Gastric Band (LAGB) (Fig 1)	Biliopancreatic diversion (BPD) +/- duodenal switch(DS)(Fig. 3a,b)	Roux-En-Y Gastric Bypass (RYGB) (Fig. 4)
Sleeve Gastrectomy(SG)(Fig 2)		

molecules such as oxalate. The result of this is an increased risk of urinary oxalate stone formation, with one study finding a fairly high prevalence of oxalate nephrolithiasis of 4% in patients post-RYGB, with an average time to stone formation of 2.9 years following surgery [48].

5.2 Laparoscopic Adjustable Gastric Banding

The operation involves laparoscopic insertion of an inflatable band, which is secured around the top of the stomach, creating a small pouch (approximately 50 ml) to receive food (Fig. 1); in this way early satiety is achieved.

There is no disruption to the natural passage of the digestive tract and no effect on absorption so nutritional deficiencies observed are generally a consequence of inadequate intake [49,50].

5.3 Biliopancreatic Diversion +/- Duodenal Switch

This procedure results in more significant malabsorption than a gastric bypass. The operation involves distal gastrectomy, jejunal transection and Roux-en-Y reconstruction with a very short efferent limb (50-100 cm). A variant of this procedure includes a duodenal switch; a vertical gastric pouch is created with preservation of the proximal 5cm of duodenum, preserving normal gastric emptying and improving iron and calcium homeostasis (Fig. 3).

This procedure results in the most rapid and sustained weight loss due to significant fat malabsorption with only 28% of ingested fat and 57% of ingested protein was being absorbed post-operatively [51]. However the technique of the procedure may have altered since this study was published. Fat soluble nutrients, including vitamin D, are malabsorbed, resulting in secondary hyperparathyroidism. Hypocalcaemia is also a problem, with an incidence of 20-48% [42,52]. Reduced bone cortical thickness at the iliac crest 10 years post-operatively has been observed [52].

Postoperative significant malnutrition and increased morbidity and mortality when compared with the other weight loss surgeries make these procedures unpopular except for the super-obese.

5.4 Laparoscopic Sleeve Gastrectomy

LSG involves removing the greater curvature of the stomach, from the Angle of His to the distal antrum, reducing stomach capacity by approximately 80% to a volume of 150-200 ml (Fig. 2). It is often used as a first-stage procedure for super-super-obese (BMI>60), patients, followed by either RYGB or DS [53].

This restrictive procedure has a similar risk profile to LAGB for post-operative nutritional deficiencies. However, with resection of the gastric fundus, the risk of vitamin B12 (and iron) malabsorption is higher [54]. There is limited data regarding the long term effect on bone health. Aarts et al. [54] found calcium levels at one year were unaffected, however 39% of patients had elevated PTH levels and 39% were vitamin D deficient; 9% were found to be vitamin B12 deficient.

6. POSTOPERATIVE PRESENTATION OF METABOLIC BONE DISEASE

6.1 General Symptoms and Signs

Unfortunately the hallmarks of almost all micronutrient deficiencies are vague symptoms. Clinical presentations such as hair loss, muscle pains, dry skin or fatigue often stretch out over months or years and patients may be diagnosed with a variety of conditions such as fibromyalgia, rheumatoid arthritis, polymyalgia rheumatica, Paget's disease and depression [55]. A study investigating patients in the first postoperative year after bariatric surgery found 28-59% reported symptoms of micronutrient deficiency [56].

In metabolic bone disease, these vague symptoms precede pathological fracture or other serious clinical sequelae so anticipation of nutritional deficiencies and prevention are key to management.

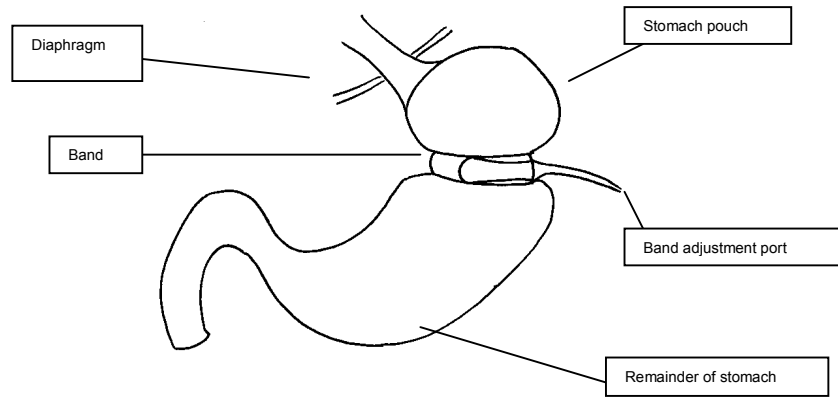


Fig. 1. LAGB

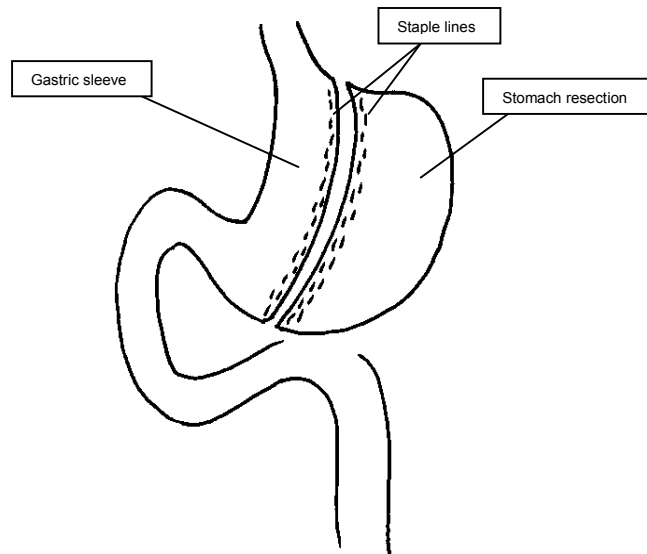


Fig. 2. SG

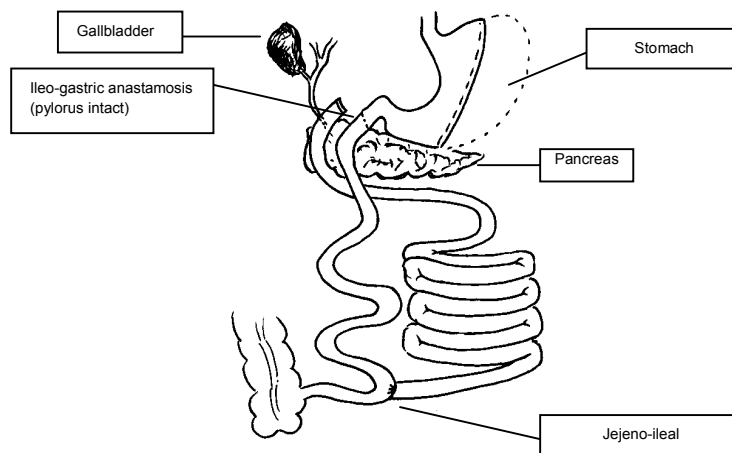


Fig. 3a. BPD with DS

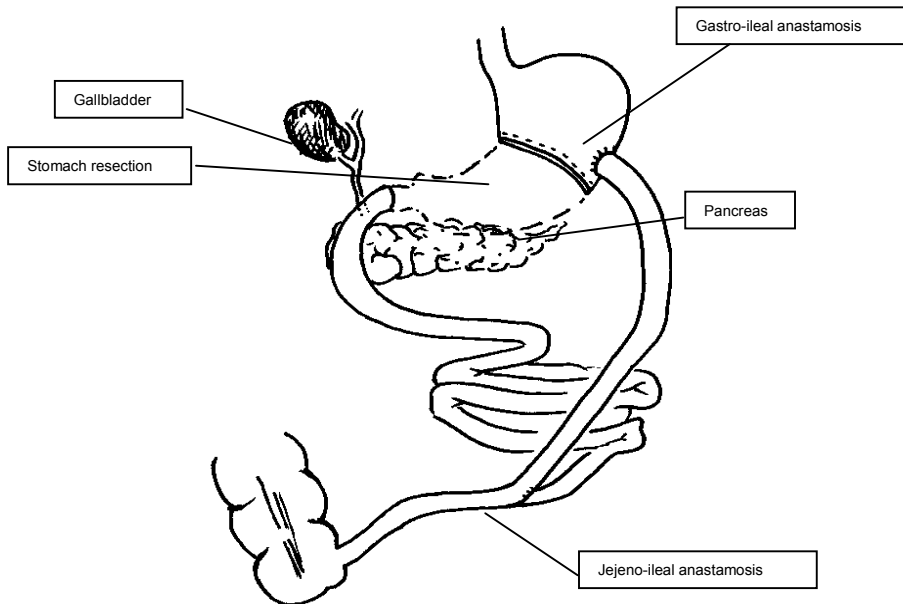


Fig. 3b. BPD without DS

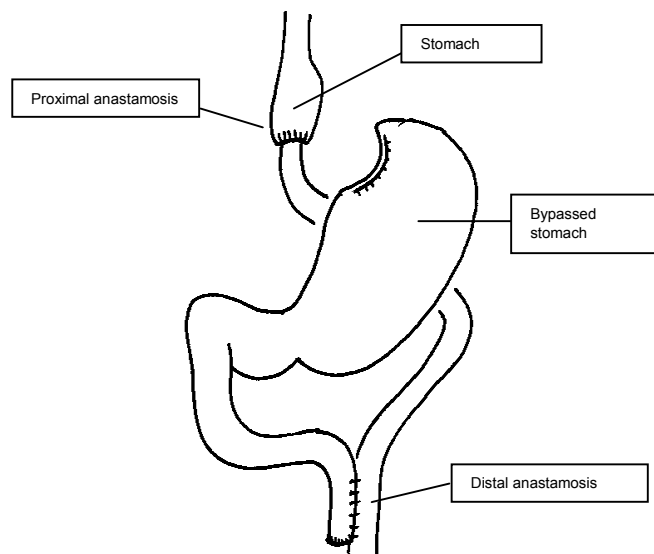


Fig. 4. RYGB

There are examples of these unusual presentations in the literature, including a case of a patient who presented with chronic pain five years post-RYGB and was diagnosed with a variety of conditions, including lymphoma for which she received chemotherapy, which in retrospect were more likely due to metabolic bone disease [17].

6.2 Impact on Bone Disease

As bariatric surgery is a relatively recent innovation, there are limited follow up data regarding the incidence of long-term sequelae such as pathological bone fracture. However a cohort study has demonstrated that gastrectomy with Billroth II reconstruction, which has similar metabolic effects to a RYGB, has a 3.6-fold increased risk of vertebral fracture compared with community residents [57].

In a study of 167 patients post-RYGB, with a mean age 47 years, found a fracture incidence of 5% within a mean post-operative follow up period of 2.4 years [58]. Brown et al. [59] reported on a case of a 46 year old woman who presented with a pathological fractured neck of femur 11 years following gastric bypass surgery. A 2% incidence of bone fracture has been observed post-BPD [52].

Despite limited data on end outcomes so far there are clear effects of bariatric surgery on BMD, so the risk of pathological fracture must be taken seriously. Appropriate prophylactic therapy is required to prevent clinical sequelae of metabolic bone disease.

7. RECOMMENDED MANAGEMENT

Bariatric surgery patients require lifetime surveillance, and recommendations have been outlined in the American Society for Metabolic and Bariatric Surgery's: (AACE/TOS/ASMBS) 'Joint medical guidelines for clinical practice for the peri-operative nutritional, metabolic and nonsurgical support of the bariatric surgery patient' [34]. The key to avoiding the development of metabolic bone disease is an active approach involving pre-operative screening, the use of appropriate and feasible monitoring modalities and adequate nutrient supplementation to combat anticipated micronutrient deficiency. Lifestyle factors must also be considered with emphasis on patient compliance and cooperation in the postoperative management process.

7.1 Preoperative Screening

Modifiable risk factors should be addressed preoperatively. Screening for micronutrient deficiencies should be performed, including vitamins C, D and B12, calcium, magnesium, zinc and iron, and then any deficiency should be rectified with supplementation [34].

7.2 Lifestyle Measures

General measures should be advised, with continuing attention to modifiable risk factors, especially smoking and sunlight exposure. If a patient is identified as having an increased risk of falls then appropriate risk management strategies should be implemented to combat the associated risk of pathological bone fracture [36].

7.3 Nutrient Supplementation

There are a variety of recommendations regarding appropriate calcium and vitamin D supplementation postoperatively to prevent metabolic bone disease. Vitamin D supplementation must be aggressive and tailored according to individual patient response. Doses less than 1000 IU/day are inadequate [60,61]. A prospective randomised clinical trial sought to find the optimal vitamin D dose post-RYGB, and found 5,000 IU per day a safe and appropriate regime for most patients. However some patients had a suboptimal response and doses of up to 50,000 to 150,000 IU may be required with more resistant cases requiring administration of oral calcitriol (1,25-dihydroxyvitamin D) [34]. There is conflicting evidence to suggest whether ergocalciferol (D2) or cholecalciferol (D3) is superior. A pilot treatment study by Stein et al. [19]. Found that cholecalciferol may be more effective in lowering PTH, however both were as effective in raising vitamin D concentrations. Vitamin D must be supplemented in isolation as adequate supplementation as a multivitamin may lead to vitamin A toxicity [27].

Ultimately exposure to sunlight is still the best source of vitamin D, and this should be reinforced as part of the patient education.

AACE/TOS/ASMBS guidelines recommend 1.2 to 1.5g of calcium supplementation daily. This should be even higher following BPD procedures, with a recommended dosage of at least 2g daily [34]. It is generally considered that calcium citrate is safer than calcium carbonate, as the latter increases the risk of milk-alkali syndrome [62]. It has been questioned whether gastric acidity aids calcium resorption by mobilising calcium from insoluble complexes in food. With this in mind it is possible that postoperative use of proton pump inhibitors may reduce resorption. Animal studies have not supported this theory but there are no data available in humans [63]. An adequate level of calcium supplementation is also important in reducing urinary oxalate excretion, and therefore reducing the risk of oxalate nephrolithiasis [34].

Vitamin B12 deficiency should be avoided with oral supplementation of 350 mcg daily [64]. Intramuscular injections at 1-month and 3-month intervals may also be used [65]. There is relatively little data to support routine supplementation of magnesium in excess of that which is included in a mineral-containing

multivitamin which provided recommended daily intake (>300 mg in women, >400 mg in men) [34].

Given the high level of osteoclast activity seen after RYGB surgery, it has been postulated that bisphosphonate therapy may prevent bone loss [34]. Preliminary data suggest bisphosphonate therapy may preserve bone mass in postmenopausal women post bypass surgery, with 2 year follow up data revealing an increase in BMD and reduced incidence of fractures as compared with a solely vitamin D/calcium supplementation group [66]. If patients meet standard requirements for bisphosphonate therapy, i.e. there is clinical and radiological evidence of osteoporosis, then treatment may be commenced. Oral bisphosphonates, particularly alendronate, are linked with risk of pill oesophagitis, ulceration and stricture formation, therefore intravenous treatment is recommended [34,67].

Patient education is essential in ensuring compliance with treatment regimens as levels of non-compliance reach 40-80% [68,69].

7.4 Postoperative monitoring

AACE/TOS/ASMBMS guidelines have given recommendations regarding postoperative biochemical monitoring, which includes routine blood tests every 3-6 months in the first year. This includes measurement of the full blood count, electrolytes, liver function tests, glucose, bone and iron studies, lipid profile and vitamin B12 levels. After 1 year, follow-up depends on the type of surgery; monitoring post-BPD is recommended every 3-6 months depending on symptoms, as compared to yearly post-RYGB. Furthermore metabolic bone evaluation is advised only post-BPD, including intact PTH, 24-hr urinary calcium and osteocalcin as needed [34].

As levels of bone turnover markers, such as ALP and osteocalcin, tend to be the first to be affected in MBD, these would be more usefully used as a screening tool to detect the disease early and in conjunction with other investigations, provide continuing monitoring and management as appropriate [49]. It is unclear at what stage these markers are initially affected in MBD and this would be an interesting field for further research.

Any changes in serum assays need to be interpreted appropriately, taking into account supplementation dosages, and thus avoiding missing an alternative diagnosis. For example if PTH levels are persistently raised, despite repleted vitamin D levels, then the possibility of primary hyperparathyroidism should be considered when associated with increased calcium levels [34].

Until reliable biomarkers are developed, early identification of osteopenia, prior to fractures occurring, is essential. DEXA bone scanning provides objective scoring of BMD. DEXA data can be combined with clinical data to provide future risk of pathological fracture. The International Society for Clinical Densitometry (ISCD) and National Osteoporosis Foundation (NOF) advise that patients undergoing a RYGB/BPD require a DEXA scan at baseline and 2 years follow up [34]. In centres where bone scanning is less readily available, it has been suggested that periodic hip X-rays could be performed to detect early changes of osteopenia [20].

A summary of recommendations based on the evidenced reviewed is shown in Table 2. Given the prevalence of metabolic bone disease post-RYGB seen in this review, we suggest more regular and thorough surveillance for metabolic bone disease in these patients.

Table 2. Summary of recommendations

Nutrient	Form	Dose	Monitoring
Vitamin D	Cholecalciferol/Ergocalciferol	5,000 IU (up to 150,000 in resistant cases)	1 st year: every 3-6 months
Calcium	Calcium citrate	1.2 – 1.5 g (up to 2 g post-BPD)	2 nd year onwards: RYGB – annual
Vitamin B12	Oral vit B12	350 mcg	BPD – every 6 months
Magnesium	As part of mineral-containing multivitamin tablet	300 mg♀ / 400 mg♂	

8. CONCLUSION

Bariatric surgery is becoming an increasingly prevalent management option for rapid and sustained weight loss in the obese population. The evidence presented in this review suggests that malabsorptive elements of the varying procedures have an impact on bone homeostasis, and may increase the risk of developing metabolic bone disease. More prolonged follow up will determine the true clinical impact, particularly with regards to premature pathological fracture. Nonetheless, clinicians caring for these patients should be aware of the implications of surgery on bone health, particularly following RYGB and be sure to implement appropriate monitoring and supplementation strategies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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