Thin bones: Vitamin D and calcium handling after bariatric surgery

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ABSTRACT

Bariatric surgery has proven to be a valuable treatment option for morbid obesity. However, these procedures can lead to impaired intestinal absorption of calcium and vitamin D, thereby challenging calcium homeostasis and possibly contributing to bone loss leading to an increased fracture risk. Besides calcium and vitamin D malabsorption, hormonal changes occurring after surgery can also be the source of observed bone loss. In this review, first, a case report will be discussed, highlighting the relevance of this topic. Afterwards, changes in bone density and fracture risk, after the two most performed types of bariatric surgery, Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) will be discussed. In addition, we discuss the putative underlying mechanisms leading to bone changes based on both preclinical and clinical observations. Nonetheless, it is clear further research is needed to further elucidate the exact mechanisms of bone loss following bariatric surgery and subsequently identify potential treatment options for bone preservation.

1. Case report

A 41-year-old non-smoking male patient was referred to our outpatient clinic because he collapsed on the street and was unable to stand up again. He had been complaining of increasing back pain for the last months. An X-ray revealed multiple vertebral compression fractures (thoracic vertebrae 10, 11, 12 and all lumbar vertebrae) and a fracture of the sixth left rib. Two years earlier, he had undergone a surgical procedure known as a biliopancreatic diversion according to Scopinaro, which is a combination of a restrictive and malabsorptive surgery, in order to lose weight. Blood tests revealed an extremely low 25-hydroxyvitamin D (25(OH)D) level at 3.8 μg/L and a low serum calcium and phosphorus level at 6.18 mg/dl and 2.11 mg/dl, respectively. The protein serum level was also decreased at 51 g/l. The serum level of parathyroid hormone was elevated at 151.4 ng/L. A bone density measurement revealed a T-score of −3.69 at the lumbar level (L2–L4) and −2.37 at the femoral neck. Initially, he was supplemented with oral vitamin D without success and subsequently intramuscular injections of Cholecalciferol were given in order to restore normal vitamin D levels. A 72 h faeces collection revealed extreme steatorrhea with a total faeces volume of 756 g/day with 76.8 g of fat/day. Consequently, treatment of pancreatic exocrine insufficiency was started with lipase, amylase and protease. This restored serum levels of calcium, phosphorus and vitamin D with a beneficial effect on bone mineral density (BMD).

This case study illustrates an important complication after bariatric surgery, often misdiagnosed and not linked to the surgery that was performed a few years earlier. This can lead to wrong treatments, such as bisphosphonates, inhibiting bone resorption, which in this case could lead to hypocalcemia. This highlights the need for knowledge on long-term complications arising after bariatric surgery and the need for post-surgical follow-up and attention for these issues.

2. Introduction

Obesity and overweight are defined as abnormal or excessive fat accumulation that often impairs health. Frequent health consequences are cardiovascular diseases, diabetes, musculoskeletal disorders and cancers. Over the last decades, obesity has risen to epidemic proportions and poses a health threat for the individual patient as well as a major socio-economic burden (World Health Organization, 2017). Bariatric or weight-loss surgery has proven to be a valuable treatment option for morbid obesity as it leads to manifest and sustainable weight reduction and improves more than 40 obesity-related diseases or

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conditions (Buchwald et al., 2004; American Society for Metabolic and Bariatric Surgery, 2010). Historically, bariatric surgeries have been divided into three categories: restrictive, malabsorptive and the combination of these two. Restrictive procedures, such as Sleeve Gastrectomy (SG), intentionally alter the anatomy of the gastrointestinal tract to reduce the amount of food intake. Following malabsorptive surgery, the amount of lipids and other nutrients that can be absorbed is reduced. Roux-en-Y Gastric Bypass (RYGB) is a combination of restrictive and malabsorptive surgery. Because of the limited food intake and/or malabsorption, bariatric surgery can indirectly induce nutritional deficiencies. The most common nutritional deficiencies after bariatric surgery include calcium, copper, folate, iron, vitamin B_{12}, vitamin D and zinc. These deficiencies can lead to various complications such as osteoporosis, anemia, neurologic problems, fatigue and generalized weakness. In particular, changes in calcium and vitamin D handling following bariatric surgery can induce bone loss, eventually resulting in higher fracture risk (Rousseau et al., 2016).

Bone loss is observed to some extent after every type of bariatric surgery, and several mechanisms have been proposed, which are mutually non-exclusive. The most important mechanisms are mechanical unloading of the skeleton, intestinal malabsorption of calcium and vitamin D (Wucher et al., 2008) and hormonal changes in response to the reduced caloric intake and the resulting energy deficit after surgery. These hormonal changes include reduced sex steroid production (testosterone and oestradiol) (Sainsbury and Zhang, 2012) and alterations in the secretion of gut-derived (Glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and ghrelin) and adipocytic (leptin and adiponectin) hormones (Sainsbury and Zhang, 2012; Brzozowska et al., 2013).

In this review, we will provide a comprehensive overview of alterations in bone metabolism following the currently most performed bariatric procedures, namely SG and RYGB. First, we will discuss the consequences of SG and RYGB on bone mass and risk of fractures, based on pre-clinical and clinical data. Next, we will discuss whether changes in bone resorption or rather formation lead to bone loss after surgery and what the possible underlying mechanisms are.

3. Effect of bariatric surgery on BMD and fractures

Several clinical studies have reported lower BMD after bariatric surgery, in particular when the duodenum is bypassed, like in RYGB (Fig. 1). Indeed, the duodenum is the site where active calcium transport can be enhanced to achieve sufficient calcium absorption when dietary calcium intake is low. After RYGB, bone loss is consistently observed during the first two years (Campanha-Versiani et al., 2017; Frederiksen et al., 2016; Obinwanne et al., 2014; Casagrande et al.,

Fig. 1. Sleeve Gastrectomy (left) and Roux-en-Y Gastric Bypass (right).

2012; Shanbhogue et al., 2017; Yu et al., 2015; Bazzocchi et al., 2015; Kaulfers et al., 2011; Maghrabi et al., 2015; Carrasco et al., 2014; Vilarrasa et al., 2013; Muschitz et al., 2016; Hsin et al., 2015; Muschitz et al., 2015; Bredella et al., 2017). Longer follow-up for three to six years still showed persistent bone loss, although the number of studies is limited (Rousseau et al., 2016; Vilarrasa et al., 2013; Elias et al., 2014; Raoof et al., 2016). After SG, which only reduces the stomach volume, it is generally considered that the effects on the skeleton would be less pronounced than after RYGB. However, recent studies seem to refute this hypothesis as not only RYGB, but also SG appears to have detrimental effects on bone density. It is, however, important to note that at this moment the studies on SG are still limited, both in terms of duration of follow-up and sample size (Maghrabi et al., 2015; Carrasco et al., 2014; Vilarrasa et al., 2013; Muschitz et al., 2016; Hsin et al., 2015; Muschitz et al., 2015; Pluskiewicz et al., 2012; Adamczyk et al., 2015a; Adamczyk et al., 2015b; Ruiz-Tovar et al., 2013). Nevertheless, most studies on SG reported decreased BMD (Maghrabi et al., 2015; Carrasco et al., 2014; Vilarrasa et al., 2013; Muschitz et al., 2016; Hsin et al., 2015; Muschitz et al., 2015; Pluskiewicz et al., 2012; Adamczyk et al., 2015a), whereas two studies described an opposite trend with increased BMD (Adamczyk et al., 2015b; Ruiz-Tovar et al., 2013). A possible explanation for this discrepancy is that Adamczyk et al. investigated solely men, and this observation might indicate sex-dependent responses (Adamczyk et al., 2015b).

At present, most studies focused on BMD and much less on fracture risk, which is, however, an important clinical outcome. Only a limited number of studies have followed up fracture risk after bariatric surgery on the long-term, until 12 to 14 years (Rousseau et al., 2016; Nakamura et al., 2014; Lu et al., 2015). Although all three studies used different control groups, comprising comparison to the general population (Nakamura et al., 2014), obese individuals (Lu et al., 2015) or both obese and non-obese persons (Rousseau et al., 2016), they consistently showed an increased fracture risk ranging from 1.2 to 2.3 fold. Interestingly, two studies that followed mainly patients after adjusted gastric banding for 4 to 5 years, found no relation with fracture risk or only an increased trend, when compared to a matched control group (Lalmohamed et al., 2012) or obese control group (Douglas et al., 2015). These findings indicate that the restrictive procedure of gastric banding likely induces less harmful effects than malabsorption procedures (Lalmohamed et al., 2012; Douglas et al., 2015).

Research in animal models supports the findings in humans. Studies in rats (Abegg et al., 2013; Stemmer et al., 2013; Canales et al., 2014) and mice (Yu et al., 2016a) found manifest bone loss after RYGB, even when comparing to body weight-matched animals (Abegg et al., 2013). With respect to SG, relatively little is known in animals, although some data suggests limited to no bone loss, in contrast to RYGB (Stemmer et al., 2013).

Taken together, most clinical and preclinical studies point towards bone loss and increased fracture risk after RYGB and SG, which is, however, less pronounced after purely restrictive procedures such as banding.

4. Bone loss after bariatric surgery: resorption versus formation

Bone is continuously remodeled during adult life by local cycles of bone resorption followed by bone formation. In order to preserve bone mass, bone resorption has to be balanced by bone formation and bone loss occurs when bone resorption outpaces bone formation. Each of these two processes can be assessed by analyzing specific bone turnover markers in serum. To assess bone formation, osteocalcin (OC) and N-terminal propeptide of type 1 procollagen (P1NP) are used as biomarkers. OC is a bone-specific protein produced by active, mature osteoblasts when they synthesize bone matrix, and increased OC levels therefore correlate with bone formation (Hauschka et al., 1989). Although OC remains a good marker for bone formation, it primarily functions as a hormone by stimulating β-cells to release insulin and
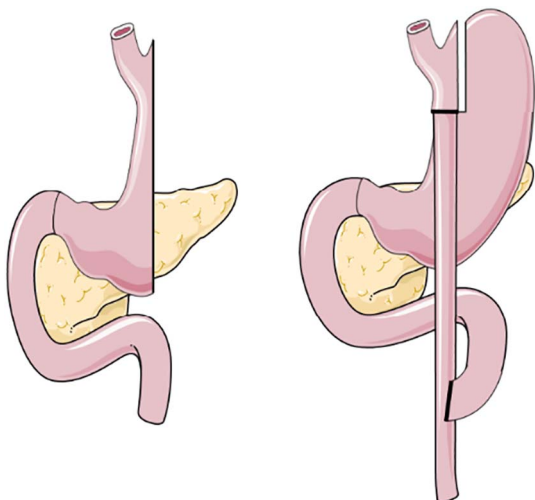
white adipocytes to produce adiponectin, which on its turn increases the sensitivity to insulin (Karsenty and Ferron, 2012). The bone formation marker P1NP also reflects bone matrix formation, as it is cleaved from type 1 procollagen during its extracellular processing and assembling into collagen fibrils, which are then incorporated into the bone matrix. A useful marker for bone resorption is C-terminal telopeptide of type I collagen (CTX-1), as it is formed by proteolytic cleavage of collagen when osteoclasts degrade the bone matrix (Szulc et al., 2017). Another marker of bone resorption is Tartrate-resistant acid phosphatase (TRACP) 5b. This form of TRACP enzyme is highly expressed in osteoclasts (Halleen et al., 2006). These serum markers help to evaluate the degree of bone resorption versus bone formation after bariatric surgery and assist to determine the types of changes in bone turnover that lead to bone loss. For RYGB, numerous clinical studies showed major increases in bone resorption markers such as CTX and TRACP 5b, but only small increases in bone formation markers P1NP and OC (Obinwanne et al., 2014; Casagrande et al., 2012; Shanbhogue et al., 2017; Yu et al., 2015; Muschitz et al., 2015; Bredella et al., 2017; Elias et al., 2014; Yu et al., 2016b; Ivaska et al., 2017; Stein et al., 2013; von Mach et al., 2004; Coates et al., 2004; Riedt et al., 2006; Riedl et al., 2008; Fleischer et al., 2008; Carlin et al., 2009; Bruno et al., 2010; Yu et al., 2014; Sinha et al., 2011; Yu, 2014; Biagioni et al., 2017; Hofsø et al., 2016). After SG, an increase in resorption markers has also been noticed, however this was less pronounced than after RYGB (Muschitz et al., 2015; Bredella et al., 2017; Ivaska et al., 2017; Stein et al., 2013; Schollenberger et al., 2015). Taken together, the present studies point towards a high bone turnover with unbalanced increased bone resorption after bariatric surgery.

5. Potential mechanisms underlying bone loss after bariatric surgery and possible therapeutic targets

In the next section, four possible mechanisms underlying bone loss after bariatric surgery will be discussed. First, the effect of mechanical unloading will be considered as weight loss is substantial after surgery, thereby decreasing mechanical loading. Secondly, the contribution of calcium and vitamin D malabsorption, with effects on parathyroid hormone (PTH) will be discussed. Thirdly, the role of the local Wnt signaling on bone mass will be considered. Lastly, the connection with adipose tissue, either through changes in adipokines or local alterations in the bone marrow, will be reviewed.

5.1. Mechanical unloading

After bariatric surgery, body weight decreases up to 30%, indicating that the mechanical load on the skeleton is also reduced. Theoretically, this lower mechanical load can lead to less bone formation, increased bone resorption and thus decreased BMD, as has been observed in other models of mechanical unloading (Komori, 2015). However, weight loss-induced bone loss is an adaptive response and might thus not evolve to

a pathological level. In addition, even when mechanical loading decreases BMD, it might not result in increased fracture risk as the load on the skeleton also decreases. Pre-clinical data also question the contribution of weight loss-related mechanical unloading, since animals after bariatric surgery have a lower bone mass even when compared to weight-matched animals, indicating that the weight loss per se is not responsible for the lower bone mass (Abegg et al., 2013). Therefore, it is unlikely that unloading-induced bone loss is avoidable or even necessary to circumvent.

5.2. Calcium and vitamin D handling

5.2.1. Intestinal malabsorption of calcium and vitamin D

Because of the alterations in intestinal anatomy induced by bariatric surgery, malabsorption of calcium and vitamin D is assumed, an effect that may contribute to bone loss. Calcium plays an essential role in processes such as muscle contraction, protein secretion, blood clotting and neuronal excitability. Serum calcium levels are therefore very tightly regulated by an interplay between the intestine, kidneys, parathyroid glands and the skeleton. The intestine is responsible for adequate absorption of calcium after oral intake, whereas the kidneys contribute to serum calcium levels by the reabsorption of filtered calcium. When intestinal and renal calcium (re)absorption is insufficient, calcium will be released from the skeleton, as it functions as a calcium reservoir, in order to maintain normal serum calcium levels. Unfortunately, the increased bone resorption needed to preserve serum calcium homeostasis will deteriorate bone quality and mass, with increased fracture risk as a consequence.

Intestinal calcium transport occurs through an active, saturable, transcellular, energy-dependent pathway as well as a passive, non-saturable, paracellular, diffusional pathway (Fleet and Schoch, 2010). In case of high calcium intake, absorption mainly occurs through passive transport, viewed as calcium diffusing through tight junctions between the cells. The amount of calcium absorbed by this pathway is directly related to the calcium concentration within the intestinal lumen and the contact time between calcium and intestinal cells (Fleet and Schoch, 2010). However, when calcium intake is normal to low, the active transcellular transport predominates. This transport mechanism consists of three steps. First, calcium enters into the cell through the transient receptors potential vanilloid type 6 (TRPV6). Subsequently, calcium is transported across the cytosol by binding to calbindin-D_{9k} and finally, calcium moves out the cell through the plasma membrane calcium ATPase (PMCA1b) into the blood (Fig. 2, left) (Bronner et al., 1986; Christakos et al., 2016). This active calcium transport is regulated by 1,25-dihydroxyvitamin D (1,25(OH)$_2$D), the active form of vitamin D. Renal calcium transport occurs in a similar manner, but with different transporters (Fig. 2, right).

Since bariatric surgery alters the anatomy of the gastrointestinal tract, it has a major influence on the biological availability of all nutrients, including calcium and vitamin D. Both, SG and RYGB lead to
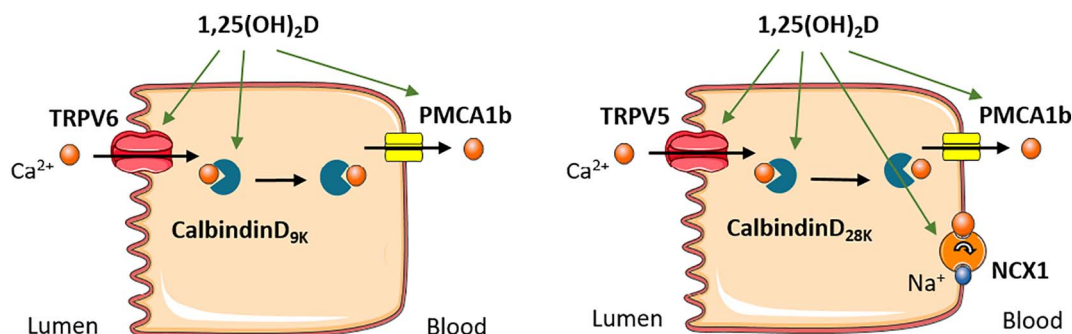
Fig. 2. Intestinal (left) and renal (right) calcium (re)absorption. Calcium is taken up by the cell through TRPV6 or TRPV5, transported in the cytoplasm bound to calbindinD_{9k} and transported across the basolateral membrane into the blood by PMCA1b or NCX1.

decreased acid secretion, which influences the disintegration and solubility of nutritional components. Additionally, RYGB influences the absorption capacity for calcium since the duodenum is bypassed and most of the active transporters for calcium are located in the duodenum and jejunum (Fleet and Schoch, 2010). Also after SG, the contact time with the intestinal mucosa is shortened, which thus may hamper nutrient absorption (Fig. 1) (Chakhtoura et al., 2016; Aarts et al., 2011). In addition, food and supplements do not mix with bile and pancreatic enzymes until the intestines join in the common channel after RYGB. This altered anatomy has major consequences for the absorption of vitamin D as it is a fat-soluble hormone and hence needs biliary acids and digestive enzymes for uptake. Moreover, vitamin D deficiency is extremely prevalent in candidates for bariatric surgery, and this presurgery deficiency further worsens after RYGB and according to some studies also after SG (Chakhtoura et al., 2016; Aarts et al., 2011; Van der Schueren et al., 2011).

To investigate the effect of the surgery-induced new anatomical situation on calcium absorption, fractional calcium absorption is used. This technique measures the percentage of an orally given dose of calcium that is absorbed. Schafer et al. recently investigated calcium absorption 6 months after RYGB surgery using dual stable isotope methodology (Schafer et al., 2015a). Despite maintaining 25(OH)D serum levels above 30 ng/ml and calcium intake at 1200 mg daily, fractional calcium absorption decreased from 33 ± 14% before surgery to 7 ± 4% after surgery, indicating a manifest reduction in the absolute amount of calcium that is daily absorbed, decreasing from 392 ± 168 mg to 82 ± 45 mg (Schafer et al., 2015a). Accordingly, 24 hour urinary calcium decreased from 191 mg to 109 mg.

In an effort to elucidate intestinal molecular mechanisms after bariatric surgery, Elias et al. investigated jejunal mucosa biopsies in patients 6 to 8 months after RYGB and vertical banded gastroplasty, who did not receive calcium supplements (Elias et al., 2014). This study revealed decreased expression of TRPV6, possibly due to reduced protein levels of heat-shock protein 90β, a co-activator of the vitamin D receptor, whereas vitamin D receptor levels were increased. These findings are consistent with the reduced calcium absorption observed at early time points after surgery (6 months, (Schafer et al., 2015a)). Nonetheless, over time, the gut may compensate for the decreased ability to absorb calcium. Indeed, TRPV6 mRNA levels were strongly increased in the jejunum and ileum of rats, 16 weeks after RYGB, which is a rather late time point (Abegg et al., 2013).

Taken together, these data suggest that adaptations in intestinal absorption occur after SG and RYGB and that it is important to elucidate the mechanisms underlying these changes. Investigating intestinal calcium absorption in detail is difficult in patients, as only minimally invasive techniques are available. Animal models can likely provide more thorough mechanistic insight into the temporal changes in intestinal calcium and vitamin D absorption that occur after bariatric surgery and that may contribute to bone loss.

5.2.2. PTH and 1,25(OH)₂D

Since normal serum calcium levels are critical for several processes, they are tightly regulated involving mainly PTH and $1,25(OH)_2D$ signaling (Fig. 3). When serum calcium levels drops, the parathyroid glands will secrete PTH. Subsequently, PTH stimulates the osteoblasts to produce the osteoclastogenic factor Receptor activator of nuclear factor kappa-β ligand (RANKL), which binds to RANK expressed on osteoclasts, thereby promoting osteoclast differentiation and survival. Osteoclasts will resorb the bone matrix and release calcium to maintain serum calcium levels in the normal range, but this occurs at the expenses of bone mass (Christakos et al., 2016). In addition, PTH activates the enzyme 1α-hydroxylase (CYP27B1) in the kidneys, which hydroxylates the inactive form 25(OH)D to its active form $1,25(OH)_2D$ (Christakos et al., 2016; Jones et al., 2014; Holick, 2016). $1,25(OH)_2D$ mediates its actions through binding to the Vitamin D receptor (VDR). As a negative feedback, $1,25(OH)_2D$ suppresses PTH synthesis and
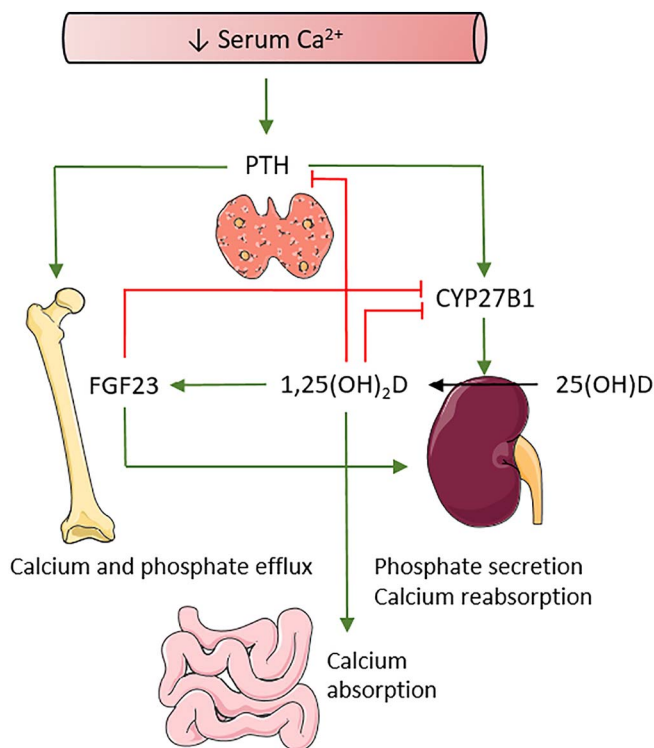

Fig. 3. Calcium and vitamin D homeostasis. PTH and $1,25(OH)_2D$ tightly regulate serum calcium levels. When calcium levels drop, PTH is secreted by the parathyroid glands. PTH will have its effects on kidneys and bone to increase calcium levels in the serum. Red lines indicate inhibitory effects, green lines indicate stimulatory effects.

reduces its own production by inhibiting CYP27B1. It also stimulates the enzyme CYP24A1, which degrades $1,25(OH)_2D$ and thus limits the amount of free circulating active vitamin D. In the intestine, $1,25(OH)_2D$ stimulates calcium absorption by increasing the expression of mainly TRPV6, calbindin-D9K and possibly PMCA1b (Fig. 2). When the supply of calcium is normal, $1,25(OH)_2D$ has no major effect on bone mass. Besides the reciprocal regulation between $1,25(OH)_2D$ and PTH, a comparable interaction exists between $1,25(OH)_2D$ and Fibroblast growth factor 23 (FGF23). Indeed, $1,25(OH)_2D$ induces FGF23 expression by osteocytes and osteoblasts. FGF23 acts as an endocrine factor by promoting renal phosphate excretion which in turn can influence PTH and calcium serum levels (Christakos et al., 2016). FGF23 signaling also inhibits CYP27B1 expression and induces CYP24A1, thereby decreasing $1,25(OH)_2D$ levels and avoiding calcium levels to rise too high (Hu et al., 2013). Together, these mechanisms allow a tight regulation of serum calcium levels.

Several clinical studies show a high prevalence of secondary hyperparathyroidism (SHPT) after bariatric surgery, which is believed to be caused by intestinal calcium malabsorption (Ybarra et al., 2005; Youssef et al., 2007; DiGiorgi et al., 2008; Clements et al., 2008; Compher et al., 2008; Valderas et al., 2009; Signori et al., 2010; Søvik et al., 2011; Grethen et al., 2011; Hewitt et al., 2013). However, the control groups in those studies often consist of normal weight individuals and not weight-matched controls which may also show high PTH levels. Indeed, a few of these studies report high PTH levels already before surgery, which would suggest that it could be obesity per se, more than the malabsorption that induces SHPT. Additionally, declines in BMD after surgery have been reported in multiple studies, even without increased PTH levels (Shanbhogue et al., 2017; Yu et al., 2015; Vilarrasa et al., 2013; Bredella et al., 2017; von Mach et al., 2004; Yu et al., 2014), further questioning whether SHPT is truly responsible for bone loss following bariatric surgery. Information on surgery-induced changes in FGF23 levels is very limited with only one study showing an increase in FGF23 after bariatric surgery in women (Grethen et al.,

2012).

Animal studies did not yet increase our insight in the importance and contribution of SHPT in the observed bone loss following surgery. Rodent studies did not find significant differences in PTH levels between bariatric groups and controls (Abegg et al., 2013; Stemmer et al., 2013; Canales et al., 2014; Yu et al., 2016a). On the other hand, Abegg et al. observed a strong induction of CYP27B1 and inhibition of CYP24A1 expression, which resulted in increased $1,25(OH)_2D$ levels, which theoretically may suppress PTH and avoid SHPT (Abegg et al., 2013).

Taken together, these findings suggest that although intestinal calcium absorption is decreased after bariatric surgery, other mechanisms than increased PTH levels seem to contribute to the observed bone loss, but the exact mechanisms remain elusive. It would be interesting to follow PTH levels longitudinally, starting from the pre-operative stage and analyzing several time points after surgery to exclude or not contribution of PTH to bone loss. At this moment, simply targeting PTH levels to prevent bone loss or titrate supplementation of calcium and vitamin D might therefore not be sufficient.

5.3. Wnt-signaling

The function of skeletal cells is not only regulated by hormones, but also by locally produced factors like regulators of Wnt signaling. This pathway affects osteoblast number, maturation and differentiation, and is inhibited by osteoblast or osteocyte secreted factors such as sclerostin and Dickkopf-1 (DKK-1). Sclerostin, encoded by the SOST gene, is produced by osteocytes and inhibits osteoblast differentiation (Muschitz et al., 2015; Viapiana et al., 2013). In mice, Sclerostin levels are down-regulated by mechanical loading and by PTH (Bellido et al., 2005; Jia et al., 2017). DKK-1 has been associated with bone resorption and osteopenia (Li et al., 2006; Li et al., 2011). Studies examining the effect of bariatric surgery on Wnt-signaling, show conflicting results. Two studies reporting decreased BMD, also found an increase of sclerostin, but, surprisingly, also a decrease of DKK-1 after SG or RYGB (Muschitz et al., 2016; Muschitz et al., 2015). Another study did not find different sclerostin levels after RYGB (Grethen et al., 2012), but BMD was not measured. Taken together, although Wnt signaling is an important pathway regulating bone mass, its contribution to bariatric surgery-induced bone loss remains elusive.

5.4. Link with adipose tissues

5.4.1. Adipokines

Bariatric surgery has a profound impact on the body fat mass and will consequently affect adipocyte-secreted hormones, i.e. adipokines. Leptin can affect bone mass by locally inducing bone formation and by a central nervous relay that activates the sympathetic nervous system (Wucher et al., 2008) and cocaine- and amphetamine-regulated transcript (CART) signaling in the hypothalamus. Studies on the role of leptin in mice resulted in discordant observations (Karsenty and Oury, 2012). A possible explanation to reconcile the data is the model stating that leptin has a complex, dual effect on the skeleton leading to increased cortical bone, but to decreased trabecular bone (Hamrick and Ferrari, 2008). In humans, a positive association of leptin and a negative association of adiponectin with BMD have been demonstrated (Biver et al., 2011; Blain et al., 2002; Pasco et al., 2001). Recent studies in mice have further elucidated that adipokines not only affect the function of skeletal cells and thereby regulate bone mass, but also control systemic mineral homeostasis. Indeed, leptin can directly stimulate FGF23 synthesis in osteocytes, whereas adiponectin decreases FGF23 release (Fig. 4) (Tsuji et al., 2010; Rutkowski et al., 2017). On the other hand, $1,25(OH)_2D$ signals to adipocytes and can enhance the production of leptin and adiponectin. Consistent herewith, vitamin D_3 deficiency is associated with low leptin levels (Wagner et al., 2017). After SG and RYGB, serum leptin levels decrease due to loss of adipose
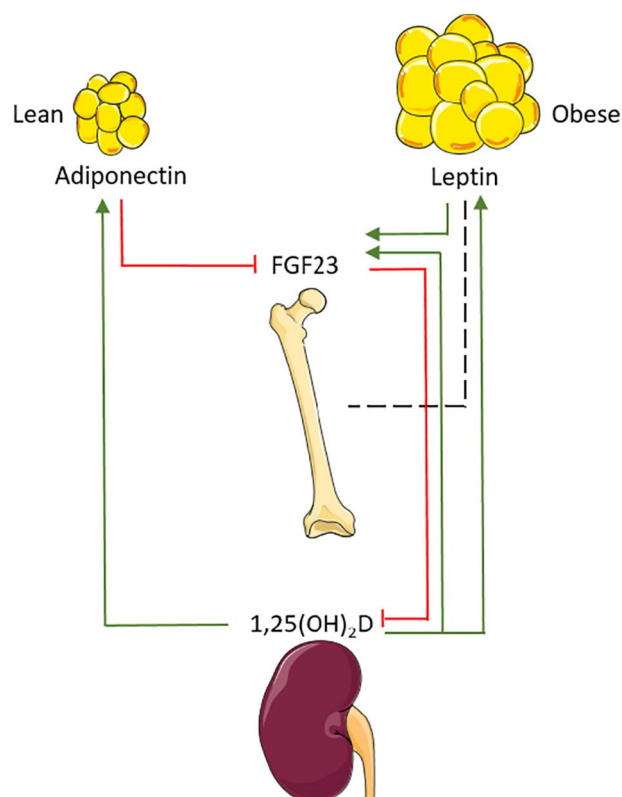

Fig. 4. The relationship between adipose tissue and bone homeostasis. Lean white adipose tissue produces more adiponectin. With obesity, adipose tissue expands and more leptin will be produced. These hormones are influenced by factors from the bone homeostasis and vice versa, as indicated by the lines. Red lines indicate inhibitory effects, green lines indicate stimulatory effects. The black dashed line indicates the relationship between bone and leptin, which is not entirely clear yet.

tissue (Shanbhogue et al., 2017; Biagioni et al., 2017; Grethen et al., 2012), whereas adiponectin levels increase (Shanbhogue et al., 2017; Carrasco et al., 2014; Biagioni et al., 2017; Grethen et al., 2012; Carrasco et al., 2009). BMD was decreased in the limited number of studies in which BMD and adipokines were measured together (Shanbhogue et al., 2017; Carrasco et al., 2014; Carrasco et al., 2009). Taken together, some correlations between levels of adipokines and bone mass after surgery have been reported, but further research is needed to explore the contribution of adipokines to surgery-induced bone loss and to hormonal changes related to mineral homeostasis.

5.4.2. Paracrine effects: local interaction between bone marrow adipose tissue and bone cells

Recently, another fat depot than white adipose tissue (WAT), has gained attention as a potential mediator of bone loss after bariatric surgery: bone marrow adipose tissue (BMAT). This hypothesis is based on research in women with anorexia nervosa in which higher levels of BMAT have been found compared to controls, although peripheral WAT is lost (Bredella et al., 2009). In mice, caloric restriction resulted in high levels of BMAT as well (Devlin et al., 2010). These findings indicate that BMAT is differentially regulated from visceral WAT and led to the hypothesis that it is used as an energy depot in the setting of starvation (Scheller and Rosen, 2014). Over the last years, BMAT has been suggested to negatively affect bone strength (Schellinger et al., 2001). Six months after RYGB, 6 diabetic and 5 nondiabetic patients showed decreased BMD with no differences between diabetic and nondiabetic patients (Schafer et al., 2015b). Interestingly, BMAT was decreased in diabetic patients, but not in the nondiabetic patients, although the overall fat mass decreased in all patients. Two other studies did not find any difference in BMAT 6 and 12 months after RYGB (Bredella et al.,

2017; Ivaska et al., 2017), although BMD was decreased after 12 months (Bredella et al., 2017). One year after SG, an increase in BMAT was observed associated with a decrease in BMD (Bredella et al., 2017), while, another study did not report these effects after 6 months (Ivaska et al., 2017). More extensive research is necessary to unravel the effect of bone marrow fat after surgery.

6. Conclusion

Over the last decades, bariatric surgery has become a very important treatment for obesity. It leads to sustained weight loss and strongly reduces the risk for obesity-associated comorbidities. However, it can also lead to nutritional deficiencies of which the long-term consequences are not fully known yet. Bone loss and increased fracture risk is often observed after bariatric surgery and requires adequate therapy. Mechanistically, calcium malabsorption and vitamin D deficiency may contribute to bone loss by inducing secondary hyperparathyroidism that increases bone resorption. However, increased PTH levels are not always detected, suggesting that also other mechanisms are involved. Possible other mechanisms that need to be explored include Wnt signaling and the connection with adipose tissue. In addition, future research needs to focus on the long-term adaptations of the body in response to the anatomical and physiological changes of bariatric surgery. Hopefully, a better understanding of the impact of bariatric surgery on the bone will indicate how to prevent or cure the bone loss.

Conflict of interest statements

The authors do not have any conflicts of interests to disclose.

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