Obesity, Bariatric Surgery, and Fractures

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Context: Obesity and its associated comorbidities are a recognized and growing public health problem. For a long time, obesity-associated effects on bone were considered to strengthen the bone, mainly because of the known relationship between body weight and bone mass and the long-term weight-bearing load effect on bone. However, recent epidemiologic studies have shown that obesity may not have a fully protective effect on the occurrence of fragility fractures. The goal of this article is to review updated information on the link between obesity, bariatric surgery, and fractures.

Methods: The primary source literature for this review was acquired by searching a published database for reviews and articles up to January 2018. Additional references were selected through the in-depth analysis of the relevant studies.

Results: We present data showing that overweight and obesity are often encountered in fracture cases. We also analyzed possible reasons and risk factors for fractures associated with overweight and patients with obesity. In addition, this review focuses on the complex effects of dramatic changes in body composition when interpreting dual-energy X-ray absorptiometry readings and findings. Finally, we review the data on the effects and consequences of bariatric surgery on bone metabolism and the risk of fractures in patients undergoing these procedures.

Conclusion: Because of various adiposity-induced effects, patients with obesity are at risk for fracture in certain sites. Bariatric surgery increases the risk of fractures in patients undergoing malabsorptive procedures. (***J Clin Endocrinol Metab*** **104: 4756–4768, 2019)**

The prevalence of overweight and obesity is increasing throughout the world. Obesity is considered to be a major international public health problem because it is associated with multiple comorbidities involving various organs such as the heart, brain, liver, lungs, vessels, joints (1), and bones (2). Overweight and obesity are defined by the World Health Organization (WHO) as an abnormal or excessive body fat mass leading to a negative impact on a person's health, or as a body mass index (BMI) $\geq$25 kg/m^2 and $\geq$30 kg/m^2 for the overweight and obesity thresholds, respectively.

According to the WHO estimates, in 2016 1.9 billion people were overweight and >650 million people obese (3). The prevalence of adult obesity in the United States as indicated by the National Health and Nutrition Examination Survey in 2007 to 2008 was 33.8% overall, 32.2% in men and 35.5% in women (4). In Europe, the prevalence of obesity has been found to be in the range of 10% to 20%

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Abbreviations: BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FLS, Fracture Liaison Service; GLOW, Global Longitudinal Study of Osteoporosis in Women; HR-pQCT, high-resolution peripheral quantitative CT; LAGB, laparoscopic-adjustable gastric band; OP, osteoporosis; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

in adult men and 15% to 25% in adult women (5). In 2013, the age-standardized prevalence of overweight and obesity combined was 55.9 (53.2 to 58.7) in men ≥20 years old and 42.8 (40.0 to 45.7) in women ≥20 years old (6).

Osteoporosis (OP) is another chronic disease, associated with increased morbidity and a higher risk of mortality. The current definition of OP characterizes this disease as a combination of low bone mass and skeletal fragility leading to an increased risk of low-trauma fractures (7). Its prevalence is rising because of the constant expansion of the older adult population. OP is now considered one of the many chronic diseases related to cellular senescence. Although there are some geographic and time trend variations, the worldwide burden of fracture is likely to increase as well (8). Until recently, obesity was believed to be protective against fracture, and accordingly a large meta-analysis of the role of BMI in the prediction of fracture (9) showed that the lower the BMI, the higher the risk of fracture. However, this paradigm has been recently challenged by several observations. The relationship between fat mass and bone is much more complex than previously thought (10), for several reasons: bone mineral density (BMD) assessment in subjects with obesity and in subjects submitted for a rapid decrease in body weight is a difficult task, prone to bias (11); the relationship between fracture risk and BMI is both age and sex dependent (12); and fracture occurrence in patients with obesity has a specific site distribution (13), with a strong role of falls (14).

Advances in surgical procedures to treat morbid obesity have led to a tremendous increase in bariatric procedures worldwide (15). Many beneficial effects of these procedures have been reported, including improved diabetes status and survival (16, 17), supporting their increasing popularity. Among these beneficial effects, the high rates of remission of type 2 diabetes mellitus (T2DM) occurring within days after surgery are the most salient (18). However, potential harmful consequences for bone health have been highlighted (11, 19, 20). In particular, the risk of fracture after bariatric procedures, which is an important clinical endpoint, is increased (21).

Therefore, the objectives of the present review were to better describe the effects of BMI on fracture risk by exploring the physiopathogenic hypotheses underlying the link between obesity and the occurrence of fracture at specific bone sites, to summarize the latest epidemiologic data on fractures in overweight and obese populations, to stress the difficulties in assessing bone density parameters in patients with obesity and to address the issue of fracture risk in patients undergoing bariatric surgery.

For this article, the PubMed database was reviewed from January 2004 to January 2018; the authors used the search terms "obesity," "fracture," "BMD," "bone loss," "weight loss," "body composition," "DXA," "osteoporosis," and "bariatric surgery." These terms were used in various combinations. Our search was limited to English-language publications. Whenever possible, priority was given to evidence from randomized control trials or meta-analyses. References from the articles retrieved and publications in the authors' library were also used.

Effect of BMI on Fracture Risk Is Not Linear

Low BMI and low weight have been demonstrated to be strong risk factors for future fracture, whereas a high BMI appeared to be protective against fractures (22–27). Both BMI and weight are documented to be good predictors of fracture in studies of forearm fractures (26) and hip fractures (27, 28). BMI was included as a continuous variable in the WHO Fracture Risk Assessment Tool (FRAX^{TM}) because it provides less variation than weight and height ranges from different countries. However, the association between BMI and fracture risk is not linear. It has been confirmed that low BMI is associated with an increased fracture risk (9), but after adjustment for BMD the association between the risk of hip fracture and low BMI disappeared (9). The relationship between BMI and relative fracture risk adjusted for either current age or BMD is characterized by an inflection point ~22 kg/m^2, with a higher risk ratio for the lower BMI values and smaller risk ratio >25 kg/m^2 (9). In fact, it has been shown that the association between BMI and fracture risk is complex and may also depend on the skeletal site considered and the interaction between BMD and BMI (29). An extensive meta-analysis including 25 prospective cohort studies from different countries revealed the complex interaction between BMI and fracture risk in women but confirmed the protective role of high BMI against the occurrence of some fractures (29).

A nonlinear relationship between BMI and pelvic fracture is also illustrated in the work of Compston *et al.* (30), with an inflection point around 30 kg/m^2.

In fact, after adjustment for BMD, a BMI >30 kg/m^2 may be associated with an increase in the risk of fragility fractures (29), and women with severe obesity who have the lowest BMD values, despite these being almost normal, have an elevated risk of fracture compared with those with higher BMD (31).

In men, the relationship between BMI and fracture risk is nonlinear, as in women, with the highest risk of hip fracture occurring in men with low BMI (32). In the Osteoporotic Fractures in Men study, in men aged ≥65 years, obesity was associated with a higher incidence of nonspine and nonhip fractures when compared with normal-weight men after adjustment for hip BMD (33).

Overweight and Obesity Are Often Encountered in Fracture Cases

The association between obesity and fractures has been reported predominantly in postmenopausal women, and less is known about obesity and fractures among men. The first evidence of a nonprotective effect of obesity with a site-dependent association as regards the occurrence of fragility fractures is recent (12, 13, 32, 34–36). The initial finding from an audit of a Fracture Liaison Service (FLS) at Addenbrooke's Hospital in Cambridge (n = 799 women) showed that 27.7% of postmenopausal women with a clinical fragility fracture managed by the FLS were obese or morbidly obese (37). The proportion of women with fracture in the BMI range 25 to 29.9 kg/m^2 was 36.9%, whereas it was 35.4% for women whose BMI was ≤25 kg/m^2 (37). It is noticeable that because of the age at inclusion in this study (<75 years), the sites of reported fractures were not the usual sites of fragility fractures (37). These data were confirmed in a cross-sectional analysis of the data from the Nottingham FLS, where a 30% prevalence of obesity was observed among participants (38). We have to analyze these data from the viewpoint of the increasing prevalence of overweight and obesity and aging of the general population; although the incidence of fracture is higher in people with the lowest BMI, most fractures occur in heavier people, as illustrated in Fig. 1. Rather than an increased risk associated with obesity, what should be emphasized is the lack of the supposed protective effect on fracture risk that a high BMI has compared with a normal BMI.

In an analysis aiming to describe the separate and combined effects of physical activity and obesity on the incidence of hip fracture in postmenopausal women from the Million Women Study, the authors found, based on their 2582 hip fractures, that women who were overweight or obese were at a reduced risk of hip fracture (39). Although 39.7% of women with incident cases of hip fracture had a BMI >25 kg/m^2, an inverse relationship was observed between BMI and the relative risk of hip fracture (39).

In the Global Longitudinal Study of Osteoporosis in Women (GLOW) aged ≥55 years, fractures in women with obesity accounted for 23% and 22% of all prevalent and incident fractures, respectively. Fracture prevalence and incidence according to BMI in the GLOW study were similar between women without obesity and women with obesity (40).

In a cross-sectional study conducted in Brazil, the prevalence of fracture was slightly higher in postmenopausal women with obesity than in nonobese postmenopausal women (17.3% vs 16.0%). In addition, 42.2% of major fractures occurred in women with obesity, supporting the concept that obesity is not protective against fracture (41).

In a population-based study including 258 residents of Olmsted County, Minnesota (82% women), average age 44 ± 10 years and mean BMI 49.0 ± 8.4 kg/m^2, who underwent bariatric surgery, 36% had already experienced a fracture before surgery, confirming that even morbid obesity does not have a protective effect against fracture (42). Although it cannot be excluded in this young population that some of the fractures reported were traumatic ones, 41.7% of the spine fractures were spontaneous vertebral fractures.

In an analysis of the National Health and Nutrition Examination Survey I, 46% of hip fractures were

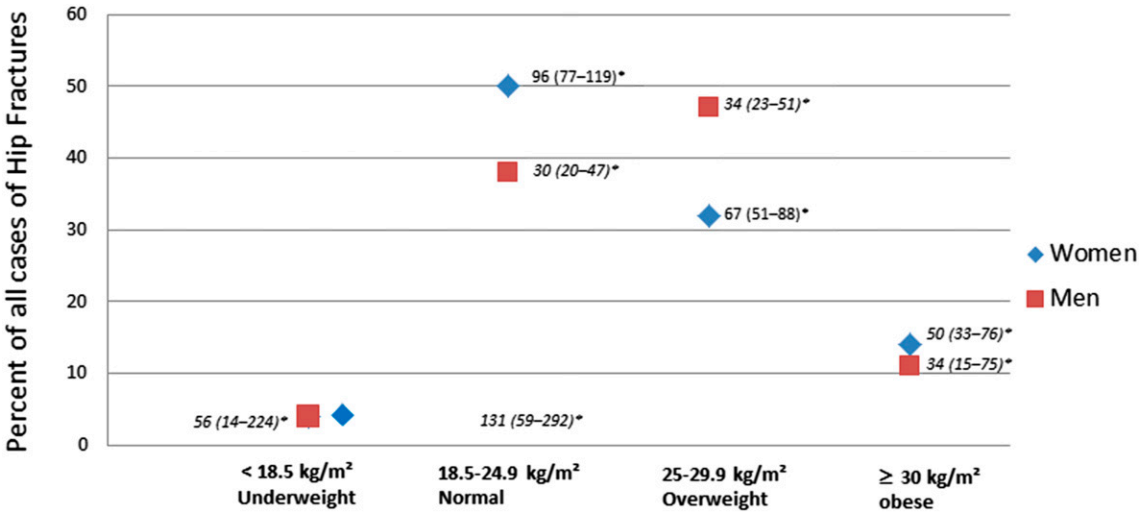

Figure 1. Hip fracture by BMI category in the National Health and Nutrition Examination Survey and National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (ages 65–74 years). *Age-standardized incidence (95% CI). [Data derived from Nielson CM, Srikanth P, Orwoll ES. Obesity and fracture in men and women: an epidemiologic perspective. Journal of Bone and Mineral Research 2012; 27(1):1–10.]

experienced by women who were obese or overweight; among men, obesity was found in 58% of men with fracture, and the majority of men >65 years with hip fracture were obese or overweight (12). At first glance, these results (39–41) may appear discrepant. In fact, we must distinguish between typical osteoporotic fractures, such as hip fractures, and the "emblematic obesity-induced" fractures such as those of the humerus, tibia, and ankles: in the former, a low BMI increases the risk, but a high BMI is only partially protective, whereas in the latter the discrepancies observed might be associated with site- and sex-specific relationships, as discussed below.

Site- and Sex-Specific Relationship Between Obesity and Fracture

Obesity- and BMI-related effects on fracture seem to be site dependent and differ across skeletal sites and sex, as illustrated in Table 1. In the largest meta-analysis examining the link between fracture risk and BMI (fractures of the skull, face, hands and fingers, feet and toes, ankle, and patella were excluded), low BMI was a risk factor for hip fracture and was associated with a lower risk for lower leg fracture, whereas high BMI was a risk factor for upper arm fracture (29).

In the GLOW, the ratio of patients with prevalent fracture was significantly higher at the lower leg and the ankle but significantly lower at the hip, rib, spine, or wrist in women with obesity compared with women without obesity (40). A significantly higher risk of nonvertebral fracture at some sites has also been reported in subjects with obesity by other authors (38, 43).

The site dependency of the complex relationship between obesity and fractures also has been highlighted in a survey of general practitioner databases from Catalonia (Spain), indicating that women with obesity could be more exposed to proximal humerus fracture (30% increase in risk) but be protected against pelvis and hip fractures (13). Consequently, depending on the fracture site, obesity might be protective or not. Consistent data concerning a lower risk of hip fracture in postmenopausal obese women have been reported (13, 39, 40).

The added complexity of the linear or nonlinear relationship between individual fracture sites and BMI has been highlighted (30, 44). Substantial differences in risk profiles among the main fragility fractures were illustrated in the work by FitzGerald *et al* (45). The most useful composite models associated with rib and pelvis fractures were those based on restricted cubic splines rather than a linear relationship.

Some sites of fragility fractures such as the ribs and the pelvis might be nonlinearly related to weight or BMI, adding more complexity to the obesity findings for fracture (30, 44).

Ankle fracture is not considered as a typical site of osteoporotic fragility fracture. In the Study of Osteoporotic Fractures, for instance, ankle fracture was not associated with low appendicular BMD at the radius, lumbar spine, or femoral neck (46).

Among the risk factors associated with ankle fracture, obesity and BMI may play a role, as suggested by a study comparing postmenopausal women with ankle fracture to a group of postmenopausal women without fracture (47). In the study, women with ankle fracture had a significantly higher weight, BMI (29.4 ± 5.4 kg/m^2 vs 26.3 ± 4.6 kg/m^2; $P < 0.001$), and the percentage of women with obesity (BMI >30 kg/m^2) was significantly higher in the ankle fracture group than in the control group (43% vs 18%; $P < 0.001$). In the Study of Osteoporotic Fractures, among the risks associated with the occurrence of ankle fracture was a history of a weight gain ≥20% compared with weight at the age of 20 [risk ratio = 1.5 (1.2 to 1.51)] (48).

For vertebrae, the data are conflicting and differ according to sex. In postmenopausal women a low BMI is associated with an increased fracture risk. However, recent studies indicate that BMI is positively associated with prevalent morphometric vertebral fracture assessed on conventional radiograph (49) and an increased risk of vertebral deformities (not clinically diagnosed) determined by vertebral fracture assessment or morphometric dual-energy X-ray absorptiometry (DXA) (34), reinforcing the message that obesity cannot be considered a protective factor against fragility fractures (2). Taking into account these specific fracture sites in obesity (ankle, proximal humerus), the following question arises: are these fractures really fragility fractures, or are they traumatic fractures associated with the higher mechanical stress exerted on bone?

In obese population, T2DM is common and contributes to the increased fracture risk (50). Site-specific differences in fracture risk are thus difficult to disentangle

Table 1. Fracture Risk in Patients With Obesity, by Sex and Anatomic Site

Sex	Increased Risk of Fracture	Protective Effect on Fracture
Women	Ankle (40)	Wrist (40)
	Upper and lower leg (40)	Hip (13)
	Upper arm (13)	Pelvis (13)
Men	Multiple rib (32)	Wrist or forearm (32)
		Hip (32)
		Pelvis (32)

between the respective roles of diabetes and obesity in associated bone fragility. T2DM increased the risk of nonvertebral fracture particularly at the hip in both sexes (50, 51). Although more frequent falls associated with T2DM may partly explain this increased fracture risk (52), they did not explain the lower rates of distal forearm fracture than those of ankle, upper arm, and hip fracture observed in population-based studies (53, 54). Additional mechanisms including unusual biomechanical loads to bone on these specific sites with insufficient bone adaptation could certainly play a role.

Pathophysiology of "Obesity-Induced Fragility": A Nonparadoxical Association

In this complex issue of the link between obesity and fracture, the role of soft tissue padding may also constitute a source of variation in the causes of fracture in patients with obesity, particularly at the hip (55). Soft tissue surrounding the hip may have two protective effects: the positive role of endogenous estrogen production via the role of aromatase in fat tissue, which is the main tissue that converts androgen into estrogen in aging people; and the role of trochanteric soft tissue thickness in reducing the load applied to the hip in a sideways fall (56). This factor has been highlighted by the reduction in hip fracture observed with the use of energy-absorbing hip pads reported in some settings (14), although this reduction in the risk of hip fracture was altered by inadequate adhesion and compliance with obese hip protectors (57). More recently, in a nested case-control study from the Framingham Osteoporosis Study, it was found that trochanteric soft tissue thickness might predict hip fracture, with a 2.4-fold higher risk of fracture for a decrease of 1 SD of trochanteric soft tissue thickness, independently of BMD (58).

Although a great body of evidence is available on the association between lean mass and bone strength (59, 60), the complex interaction between adipose tissue and bone strength has not been extensively documented (61–63). The effects of adiponectin and leptin on bone physiology are increasingly recognized (64–66). However, because of discrepant results in human studies the effects of these adipokines on bone are not fully elucidated (19).

A higher frequency of falls in women with obesity was also described in the GLOW (40). Limited mobility in people with obesity might contribute to specific patterns of falling. In the Osteoporotic Fractures in Men study, the increased risk of nonspine fractures was attenuated in men with obesity after adjustment for limitations in mobility. This impaired mobility and loss of the normal protective response to falling, with a propensity to fall sideward and backward rather than forward (67), may partly explain the site-dependent association between obesity and fracture (13).

Actually, adipocyte function is strongly related to its location; depending on whether they are peripheral adipose tissue, visceral adipose tissue, subcutaneous fat, or marrow adipose tissue, fat deposits have different influences on bone tissue cellular activities and metabolism (68, 69). Fat mass as a whole has been shown to be a consistent predictor of BMD in postmenopausal women (70) and particularly at weight-bearing sites (71). These different influences might be related to different mitochondrial activity through different expressions of uncoupling protein implicated in heat production whether brown adipose tissue or white adipose tissue is considered (72–74). Indeed, visceral adiposity has been mostly found to be negatively associated with trabecular BMD while altering bone turnover and microarchitecture (75, 76). In postmenopausal women, both total and visceral adiposity were significant predictors of prevalent vertebral fracture (77). High bone marrow fat has also been associated with low BMD and osteoporotic fractures (78, 79). By sharing their origin with the osteoblast lineage from mesenchymal stem cells, as well as through their secretory profile, marrow adipocytes closely intervene in bone remodeling (80).The obesity-induced effects on bone health are not limited to those related to the bone-fat interactions. Other pathogenic factors may participate in the mechanisms leading to bone fracture in people with obesity, including vitamin D deficiency (81), reduced mobility, inflammation, and comorbidities (82). Bone weakness has been also evidenced in patients with T2DM (a well-known comorbidity associated with obesity), and these patients are at risk for fractures despite normal areal BMD (83). Diabetes has direct deleterious effects on qualitative parameters that can compromise bone material strength (84) and contribute to an increased risk of fracture (85). Some studies have elucidated the role of higher cortical porosity in patients with T2DM with fragility fractures (86, 87), but other studies, when adjusting for BMI, did not find a significant difference for cortical porosity (84) or for microarchitecture parameters between patients with T2DM and controls (88). Obesity-induced hypogonadism (in men) may also be a contributor; indeed, it has been demonstrated that men with obesity tend to have low levels of testosterone (89). In addition, androgens via the androgen receptor in mesenchymal bone marrow progenitor cells negatively regulate fat mass and may improve metabolic function (90). Other cell types may play a role in bone metabolism alterations related to increased fat mass. Deleterious interactions between muscle function and adiposity through complex cross-

talking between these tissues via muscle fat infiltration and then insulin resistance (91) promote poor muscle strength (92) and lead to sarcopenic obesity (93). This sarcopenia could also increase the skeletal fragility of people with obesity. Finally, both bone marrow adipocyte and white adipocyte secrete adipocyte-derived proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which are implicated in the dysregulation of immune cell activities (94).

Bone Density Testing in Obese Patients

Measurement of BMD in patients with obesity is challenging

Measurement of BMD in patients with obesity is challenging and can introduce errors in both accuracy and precision as a result of the increase in fat mass and changes in its distribution. Experiments using blocks of lard to simulate body fat indicate that the effect of obesity varies according to the type of DXA system used for measurement, the distribution of body fat, the software versions used by the manufacturer, and the scan mode (95–100).

Greater BMD in obesity is not an artifact of DXA measurement

Soft tissue thickness may cause a projection error affecting measurements of bone area and thus bone mineral content. Measurements of bone density by quantitative CT and high-resolution peripheral quantitative CT (HR-pQCT) are less affected by overlying soft tissue than measurements by DXA, and bone geometry and bone microarchitecture can be assessed. Some studies have reported that adults with obesity had greater BMD at all sites measured and favorable bone microarchitecture and greater bone strength at the distal radius and distal tibia, whereas bone geometry did not seem to be modified (101, 102). In contrast, other studies have found that although a high BMI (>35) was associated with an increased trabecular volumetric BMD, in the presence of higher PTH serum level, it was inversely associated with a lower cortical volumetric BMD (103). In addition, bone material strength indices assessed at the tibia were independently and negatively associated with local adipose tissue (104).

Pleiotropic effects of obesity on fracture risk

Obesity leads to increased BMD (both areal BMD and volumetric BMD) and more favorable bone microarchitecture and strength at weight-bearing sites (greater skeletal loading) and non–weight-bearing sites. However, impact forces in a fall are greater in people with obesity because body weight is greater. To reduce fracture risk, the increase in BMD, stimulated by obesity, has to compensate for greater impact forces and possibly for impaired bone microarchitecture and bone material strength (104). The increase in bone strength is not commensurate with the increase in fall impact forces, and therefore the "bone advantage" from obesity is not sufficient to reduce fracture risk. There may be a plateau that differs for each fracture site. Finally, greater absorption of impact forces by soft tissue padding around the hip may underlie the relative reduction in hip and pelvic fracture risk in women and men with obesity, as previously indicated. Different fall directions and fall forces in obesity could also contribute to the greater risk of lower limb and proximal humerus fractures.

Impact of weight loss on bone mineral density in adults with obesity

Unlike in the total hip, no significant effect of diet-induced weight loss was observed in the lumbar spine in overweight or people with obesity. Indeed, dietary weight loss interventions were associated with a small but statistically significant reductions in total hip BMD (105). It has been postulated that changes in fat distribution can lead to alterations in bone measurement (bone area and bone mineral content) without any real change in the skeleton (BMD) (100, 106–108).

Bariatric Surgery and Fracture Risk

Morbid obesity (BMI $\geq$40 kg/m^2) or class 3, severe obesity, has followed the same dramatic rate of increase. Unfortunately, various efforts aimed at weight loss including exercise, diet intervention, and other nonsurgical procedures do not provide long-term success to reduce and maintain weight loss in people with morbid obesity. Dietary modification does not enable significant weight loss to be maintained, and successful medical management of morbid obesity by drugs is very scarce (109). Because of the low efficacy of medical treatment, surgical treatment of morbid obesity is increasingly common thanks to the development of laparoscopic surgery.

Laparoscopic Roux-en-Y gastric bypass (RYGB) is characterized by bypass of the duodenum and proximal jejunum. Laparoscopic vertical sleeve gastrectomy (80% of the stomach is removed) is now becoming the most popular bariatric procedure. Because of its limited effect on weight loss, the laparoscopic-adjustable gastric band (LAGB) is rapidly decreasing in popularity.

Other types of bariatric surgery procedures resulting in the greatest weight losses, such as biliopancreatic diversion with or without duodenal switch operations, combine both gastric reduction and extreme intestinal bypass. It has been shown that bariatric surgery has many

benefits beyond weight loss, including improved control of glycemia, blood pressure, and dyslipidemia (110). Unfortunately, bariatric surgery is also associated with complications. The medical complications include gastroesophageal reflux disease, malnutrition, and metabolic complications deriving from vitamin and mineral malabsorption. In addition, the deleterious effect of bariatric surgery on bone health remains to be acknowledged. Studies of bariatric surgery and bone outcomes are usually limited to assessment of bone remodeling biomarkers and BMD (111, 112). First, it has been reported that bariatric surgery negatively alters bone remodeling, as markers of bone remodeling are increased (112, 113). Second, bariatric surgery is associated with increased rates of bone loss (111, 112, 114–116). Third, the deleterious effect of bariatric surgery on bone health has also been demonstrated via quantitative CT (hip and spine), HR-pQCT (distal tibia and radius), and estimated bone strength in a prospective cohort study including 30 adults undergoing gastric bypass and 20 nonsurgical controls (117). Substantial bone loss, decreased bone strength, and microarchitectural alterations at all sites occurred throughout the 24 months after gastric bypass despite weight stability in the second year (117, 118). Impaired bone health increased in subsequent years up to 5 years (119). After bariatric surgery, microarchitectural deterioration (reduction in cortical area, density, and thickness) was found (120). This cortical bone loss was associated with increased PTH levels. The detrimental effects of RYGB on microarchitecture were detectable as early as 6 months after surgery (121). Decreases in cortical thickness and area associated with altered trabecular bone parameters were also described after RYGB (122). Altogether, these data demonstrated that microarchitectural alterations might be one cause of fracture risk after bariatric surgery. Hence, there is a growing body of evidence that bariatric surgery is associated with an increased risk of fracture, although the first study related to this concern (described below) was reassuring (123).

In a population-based, retrospective cohort study, data from 625 primary care practices in the United Kingdom were studied to estimate the fracture risk in patients undergoing bariatric surgery compared with age-, sex-, and BMI-matched controls (123). Data from the Clinical Practice Research Datalink included 2079 patients with morbid obesity who underwent bariatric surgery between January 1987 and December 2010. Fracture outcomes were collected as osteoporotic fracture [humerus, forearm, spine, or hip, *i.e.,* major osteoporotic fracture (124)] and nonosteoporotic fracture. However, in this study there was no information on the level of trauma; only information on fracture site was included, preventing conclusions about fracture cause. Patients were followed up for a mean duration of 2.2 years if they underwent bariatric surgery and 2.3 years for controls. No significant increase in any osteoporotic or nonosteoporotic fracture risk associated with bariatric surgery procedures was shown, probably because of the short duration of follow-up. However, a nonsignificant trend in favor of an increased risk of any fracture was observed in patients 3 to 5 years after surgery, and a nonsignificant trend toward increasing risk of any fracture was found in patients exhibiting the greatest decrease in BMI after bariatric surgery (123).

A historical cohort study of fracture incidence was conducted, based on the Mayo Clinic bariatric surgery practice database and the Rochester Epidemiology project (42). Residents of Olmsted County (n = 258) who underwent a first bariatric surgery from 1985 to 2004 were included in the study, with a median follow-up time of 7.7 years (42). Fracture events were collected from the clinical history and radiologist's report of each clinical fracture, including vertebral clinical fracture. However, radiographs were not individually analyzed. In this Minnesota population-based bariatric surgery cohort, a twofold increased risk of hip, spine, and wrist fracture was found (42). The discrepancies evidenced in the results of the fracture risk associated with bariatric surgery in the UK and Minnesota studies may appear surprising at first glance. However, one must consider that the two study designs differed: in the UK study the control group was age-, sex-, and BMI-matched, whereas in the Minnesota study cumulative incidence of fracture among patients undergoing bariatric surgery was compared with expected incidence among community men and women (42). Noteworthy in this last study, a skeletal site–specific analysis showed that the two highest standardized incidence ratios, 5.5 (1.5-= to 14) and 5.0 (2.2 to 9.9), expressing the relative fracture risk, were found at the proximal femur and humerus, respectively (two major osteoporotic fracture sites), supporting the overall result of this study showing an increase in fracture risk associated with bariatric surgery. However, the increased fracture risk observed in the Minnesota study may represent the effect of obesity-related comorbidities and not the effect of bariatric surgery *per se,* because patients were compared with the community residents.

In addition, the types of bariatric surgery preferentially used in these two studies differed: in the UK study 60% of operations were LAGB and 29% of patients underwent RYGB (123), whereas in the Minnesota study (42) the preferential bariatric surgery used was RYGB. The potential detrimental effects on bone may differ between these surgical procedures, leading to different effects on weight loss, hormonal and adipokine

perturbations, and bone loss (125, 126). Indeed, the long-term consequences of bariatric surgery on fracture risk are likely to vary by procedure type. Based on claim data from a US commercial health plan, rates of nonvertebral fractures were analyzed within a propensity score–matched cohort (n = 15,032) of morbidly adults with obesity who underwent either RYGB or LAGB surgery between 2005 and 2013 (127). Patients undergoing RYGB had a 43% higher risk of nonvertebral fracture compared with patients undergoing LAGB. In another study based on claim data from the National Health Insurance Research Database of Taiwan, rates of fractures were analyzed within a propensity score–matched cohort of morbidly adults with obesity who underwent bariatric surgery (128). At the end of the 12-year study period, there was a 21% higher risk of fracture in the surgical group compared with the control group (128).

Finally, the follow-up time was quite different in the UK and Minnesota studies: mean duration of follow-up was 2.2 years in the UK study (123) compared with a median follow-up of 7.7 years in the Minnesota study (42). Follow-up time might be of the utmost importance in determining the risk of fracture, because it was observed in the Minnesota study that more than half of the fractures occurred after 5 years (42). Confirming this hypothesis, nonvertebral fracture risk associated with RYGB manifested >2 years after surgery and increased in subsequent years, with the highest risk in the fifth year after surgery (127). Thus, the gradual increase in fracture risk over time after bariatric surgery was also illustrated in the Taiwan cohort study, with a trend of an increased fracture risk 1 to 2 years after surgery (128), and in a retrospective cohort study based on Swedish national databases, where the fracture risk also appeared to increase with time (129).

Using a retrospective nested case-control study, Rousseau *et al.* (130) demonstrated that bariatric surgery was associated with a higher risk of fracture compared with obese or nonobese controls. Fracture risk was site specific, changing from a pattern associated with obesity to a pattern typical of osteoporosis after surgery.

Finally, a meta-analysis addressing fracture risk after bariatric surgery confirmed that subjects with obesity who underwent bariatric surgery have a higher risk for any type of fracture (risk ratio 1.29; 95% CI, 1.18-= to 1.42) (21).

The deleterious effects on bone health induced by obesity and bariatric surgery are summarized in Table 2.

Conclusions

Obesity is a chronic disease with serious health consequences. There is a growing body of evidence from epidemiological studies supporting the lack of protective effect of obesity on the risk of fracture. The worldwide increase in obesity explains the contribution of fractures occurring in overweight or obese populations in the whole burden of fractures. Skeletal fragility in the obese population might be associated both with weight-dependent and weight-independent mechanisms, including the role of adipokines, visceral and bone marrow fat, noncommensurate bone mass and geometry to compensate the potentially higher forces involved in "low-energy" fractures in the obese population, and falling patterns. Bariatric surgery, which is the most effective treatment to reduce BMI and obesity-related comorbidities, produces detrimental effects on bone health, namely an increase in fracture risk. Specific prospective studies aimed at better describing the underlying mechanisms of bone fragility, both in the obese

Table 2. Deleterious Effect of Obesity and Bariatric Surgery on Bone Health

Parameter	Obesity (General Increase in Adipose Tissue)	Bariatric Surgery
Fracture risk	↓ Hip, pelvis (40) ↑ Humerus, lower limb	↑ All fractures (128)
BMD	↑ (101)	↓ (117, 118)
Markers of bone remodeling	Lower bone formation relative to resorption markers (102)	↑ (117, 118)
Microarchitecture (HR-pQCT)	↑ Tb.vBMD (101) ↑ Ct.vBMD (101)[b] ↑ Ct.Th (101) ↓ Ct.Po (101)[b]	↓ Tb.vBMD (117, 118, 121, 122)[a] ↓ Ct.vBMD (121, 122)[a] ↓ Ct.Th (120, 121, 122) ↑ Ct.Po (121)
Bone strength (microfinite element analysis applied to the HR-pQCT images) (microindentation)	↑ (101) ↓ (100)[a,c]	↓ (117, 118, 121)[a]

The ↑ symbol indicates an increase, and ↓ indicates a decrease.

Abbreviations: Ct, cortical; Po, porosity; Tb, trabecular; Th, thickness; vBMD, volumetric bone mineral density.

[a] At the tibia.

[b] Subcutaneous tibia fat was inversely associated with Ct.vBMD and positively associated with Ct.Po in older women (104).

[c] Fat mass was inversely associated with bone material strength index (104).

population and in patients who undergo bariatric surgery, might help prevent bone fragility fractures.

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