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REVIEW

The obesity paradox and osteoporosis

Angelo Fassio[1] · Luca Idolazzi[1] · Maurizio Rossini[1] · Davide Gatti[1] · Giovanni Adami[1] · Alessandro Giollo[1] · Ombretta Viapiana[1]

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Abstract
Overweight and obesity according to the definition of the WHO are considered as an abnormal or excessive fat accumulation that may impair health. Studies comparing fracture incidence in obese and non-obese individuals have demonstrated that obesity, defined on the basis of body mass index (BMI), is associated with increased risk of fracture at some sites but seems to be protective at others. The results of the studies are influenced by the distribution of BMI in the population studied; for example, in cohorts with a low prevalence of obesity, a predilection for certain fracture sites in obese individuals becomes difficult to detect, whereas, in populations with a high prevalence of obesity, previously unreported associations may emerge. Furthermore, obesity can bring with itself many complications (Type 2 diabetes mellitus, vitamin D deficiency, and motor disability) which, in the long run, can have a definite influence in terms of overall risk and quality of life, as well. This is a narrative review focusing on the relationship between bone metabolism and overweight/obesity and dealing with the fundamental dilemma of a disease (obesity) apparently associated with improved values of bone mineral density, part of a complicated relationship which revolves around obesity called "the obesity paradox".

Keywords Obesity paradox · Osteoporosis · Bone metabolism · Bone mineral density and obesity

Introduction

Osteoporosis is defined by the World Health Organization (WHO) as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [1]. Osteoporosis and its consequences, fragility fractures, represent a relevant and increasing burden involving not only critical aspects of the single subjects such as quality of life and mortality but also on healthcare systems [2]. However, data show that a large part of the patients at increased risk of fracture does not receive appropriate osteoporosis treatment [3]. Identification of the subjects at high fracture risk is of paramount importance to target appropriate treatment in a more cost-effective and precise way.

Overweight and obesity according to the definition of the WHO are considered as an abnormal or excessive fat accumulation that may impair health [4, 5]. Obesity has been defined as an epidemic, progressively worsening in the last 50 years, associated with several medical conditions [6].

Primary osteoporosis is defined as osteoporosis occurring after menopause (also known as *post-menopausal osteoporosis*) or with advancing age (*senile osteoporosis*). On the contrary, secondary osteoporosis can be a consequence of disorders of various kinds or caused by a number of dugs, as well [7]. Overweight/obesity can be found in some kinds of secondary osteoporosis, as seen in patients affected by a chronic exposure to glucocorticoids, whether it be of endogenous nature (Cushing's syndrome) or exogenous (glucocorticoid-induced osteoporosis) [7].

The performance of bone mineral density (BMD) in the prediction of fracture risk is greatly increased by the concurrent inclusion of relevant risk factors operating along with BMD in an independent way. Relevant risk factors include: age, female sex, and previous fragility fracture [7–9]. In

The original version of this article was revised: Author's first name and the family name were incorrectly swapped in the original publication and it has been corrected now.

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✉ Angelo Fassio
angelo.fassio@yahoo.it

[1] Rheumatology Unit, University of Verona, Policlinico G.B. Rossi, piazzale A. Scuro, 37134 Verona, Italy

addition, a low body mass index (BMI) has shown to be a relevant risk factor especially for hip fracture [10]. However, its value in predicting other types of fractures is much reduced when the risk is adjusted for BMD [10].

Upon these consideration, one could argue whether overweight and obesity really present a relevant role towards the increase of the fracture risk. However, as we will discuss later, there are important implications in the relationship between overweight and bone metabolism which can play a contradictory role on the final outcome. It is somewhat intriguing to realize how obesity is characterized both by a protective and a detrimental role on osteoporosis and risk of fracture. This paradox justifies the remark of the higher BMD found in obese subjects, despite the absence of a relevant protective on the risk of fracture (which, in some cases, may even be increased).

This review will discuss the various mechanisms implied in the influence between obesity and bone health.

This article is a narrative overview on obesity paradox and osteoporosis. We used as sources MEDLINE/PubMed, CINAHL, EMBASE, and Cochrane Library, from inception to 2017.

In addition, we hand-searched references from the retrieved articles and explored a number of related websites. After discussion, we chose 36 relevant papers (Tables 1, 2).

Obesity and the bone: the mechanical relationship

Interesting insights regarding the way in which obesity exerts its effects on bone metabolism can be drawn from the study of biochemical markers of bone turnover. Biochemical markers are lower in obese subjects than in lean subjects [11], and this difference may be more relevant for bone-resorption markers than bone formation ones [11]. The uncoupling of these two phenomena in obesity suggests a total positive bone balance, which may help to maintain bone mass in adulthood and with aging [12]. On the contrary, menopause brings a quick increase in bone turnover, with net higher bone resorption and negative bone balance and thus leading to bone loss. Higher body weight has been shown to slow down menopausal bone loss [13].

One mechanism able to explain the higher BMD found in obese people is the increased mechanical loading and strain associated with this condition. As a matter of fact, obese people have increased body fat mass and increased lean mass, as well; therefore not only passive loading, but also muscle-induced strain is increased. This may have effects on bone modelling, density, and geometry. However, the impair in muscle strength which is associated with the accumulation of fat in the muscle tissue [14, 15] might also attenuate the positive effects of the muscle mass and action on bone [15]. Thus, if the main mechanism acting to increase BMD was physical loading, an increase in bone size by periosteal apposition should be expected. However, as often happens when dealing with obesity, things are not so straight-forward. Indeed, even though hip cross-sectional area measured by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) is increased in obese subjects [16, 17], bone size at the radius and tibia by high-resolution peripheral quantitative computed tomography (HR-pQCT) does not differ between obese- and normal-weight controls [12]. In conclusion, the loading factor is not sufficient to explain all of the action of obesity on bone.

The bone and fat cross-talk

A key role in determining the effect of obesity on BMD is determined by the cross-talk between the bone tissue and the adipose tissue. The apparent ambiguity of the higher values in terms of BMD may be partially linked to the well-documented relationships between oestrogens and obesity. Post-menopausal women who are obese have been shown to have higher blood concentrations of oestrogen than non-obese controls [18, 19]. These remarks may explain, at least in part, not only the association between higher BMD and higher BMI, but also with the increased risk of hormone-related cancers such as endometrial and breast cancer [20]. However, oestrogen levels are not the only regulator of bone mass and, therefore, several other factors may affect both bone and fat mass. It is, indeed, intriguing the complexity of the factors that both adipose tissue and bone cells produce which are able to affect each other.

One of the endocrine actions of the adipose tissue is the production of adipokines, which regulate many metabolic processes, such as caloric intake, insulin sensitivity in peripheral tissues, etc. [21]. Adiponectin, an adipokine, that has been shown to have deleterious effect on bone [19, 22]. Adiponectin is known to be inversely related to BMI, and it is currently considered a marker of a disrupted adaptive response in overweight patients [19, 22]. In the Health Aging and Body Composition Study, serum levels of adiponectin were reported higher in overweight women with fractures when compared with overweight women without fractures [23]. Another important factor is leptin, another adipokine, which has been demonstrated to interfere with bone metabolism through different mechanisms [23, 24]. Leptin seems to act by two seemingly contradictory mechanisms. Individuals with high serum levels of leptin have increased bone mineral density as measured by DXA [23]. However, leptin acts via the central nervous system to decrease bone formation. This latter action appears to be mediated by a decreased production of serotonin in the hypothalamic neurons [24]. Moreover, adipose tissue also produces inflammatory cytokines,

Table 1 Obesity and BMD and/or fracture risk

References	Sample	Design	Results
Garnero et al. [11]	435 females, pre- and post-menopausal	Longitudinal	Low BMI is a significant risk factor for hip fracture, but the value of BMI in predicting other fractures is very much diminished when adjusted for BMD
Evans et al. [12]	100 individually-matched pairs of normal and obese men and women	Cross-sectional	Obese adults have higher BMD, thicker and denser cortices, and higher trabecular number than normal adults
Reid et al. [13]	122 normal post-menopausal women	Longitudinal	Higher body weight is associated with slower menopausal bone loss
Shen et al. [16]	3067 men (mean aged 73 years)	Cross-sectional	For non-obese men, increasing BMI was associated with higher integral, cortical, and trabecular vBMD, integral volume, cross-sectional area, and percent cortical volume. For obese men, increasing BMI was not associated with any of those parameters. Compared to non-obese men, obese men had a higher hip strength, but also a higher ratio of impact force to strength
Bachmann et al. [17]	368 women (aged 19–45 years): 246 with anorexia nervosa, 53 overweight/obese, and 69 lean controls	Cross-sectional	Femoral geometry by hip-structural analysis, hip BMD, and factor of risk for hip fracture attenuated by soft tissue are impaired in anorexia nervosa and superior in obesity, suggesting higher and lower hip fracture risk, respectively
Sukumar et al. [22]	211 women (aged 25–71 years; BMI 18–57)	Cross-sectional	Higher BMI was associated with greater values of trabecular bone and cortical BMC and area, but lower cortical vBMD
Barbour et al. [23]	3075 women and men (aged 70–79 years)	Longitudinal	Men with the highest adiponectin level had a 94% higher risk of fracture compared to the lowest tertile. Significant even after adjusting age, race, BMI, education, diabetes weight change, and hip BMD. Among women, after adjusting for age and race this association was no longer significant
Tang et al. [31]	15 prospective cohort studies involving a total 3,126,313 participants	Meta-analysis of prospective cohort studies	Obesity significantly decreases the risk of hip fracture in adults
Compston et al. [32]	60,393 women (aged $\geq$ 55 years)	Longitudinal	Obesity is not protective against fracture in post-menopausal women and is associated with increased risk of ankle and upper leg fractures
Prieto-Alhambra et al. [34]	SIDIAP database. 832,775 women (aged > 50 years)	Both longitudinal cohort and hospital admission databases as a reference	Hip fractures were significantly less common in overweight and obese women than in normal/underweight women. Pelvis fracture rates were lower in the overweight and obese groups. Obese women were at significantly higher risk of proximal humerus fracture than the normal/underweight group. Clinical spine, wrist, tibial, and multiple rib fracture rates were not significantly different between groups
Yang and Shen [35]	5287 men and women (aged between 8 and 69 years)	Cross-sectional	Greater BMI and hip circumference were associated with increased BMD at the lumbar spine and femoral neck. The remaining obesity variables were positively associated with increased femoral neck BMD only
Berg et al. [36]	2685 adults (aged 20–79 years)	Cross-sectional	BMI and waist circumference and abdominal fat volume are positively associated with bone stiffness in the general population

Table 1 (continued)

References	Sample	Design	Results
Sornay-Reundu et al. [37]	63 OB women (mean age 69 ± 8 years) age-matched with 126 non-obese women	Cross-sectional	The higher absolute values of bone densities, cortical and trabecular architecture, and strength indices were not in proportion to the excess of BMI and particularly of FM in obese post-menopausal
Chang et al. [38]	368 elderly women	Cross-sectional	Compared with the non-osteoporosis subjects, the subjects with osteoporosis had relatively higher mean age, lower body mass index, and a lower percentage of central obesity. In addition, the larger the waist circumference of obese subjects, the less likely they are of having osteoporosis
Lenchik et al. [39]	38 women and 42 men (age 39–81 years, BMI 17–55, 86% with type 2 diabetes)	Cross-sectional	After adjusting for age, gender, race, smoking, and diabetes status, serum adiponectin was inversely associated with areal BMD, volumetric, and visceral fat volume. These associations remained significant after adjusting for whole-body fat mass
Jankowska et al. [40]	272 men (aged 20–60 years)	Cross-sectional	BMI was positively related only to trabecular BMC. Only trabecular BMC was higher in men with BMI > or = 27 compared to non-overweight subjects. Waist-to-hip ratio was inversely related to trabecular, cortical, and total BMC. All densitometric parameters were lower in males with Waist-to-hip ratio > or = 0.95 than in normal men
Tseng et al. [41]	352 men (mean age 70.6+/-11.9 years) and 468 women (mean age 67.8+/-12.0 years)	Cross-sectional	In subjects with the metabolic syndrome (MS), lower diastolic blood pressure in both sexes, lower triglycerides, and more central obesity in men predicted bone mineral loss. The MS was not associated with bone mineral loss in either of sexes
Ghezelbash et al. [42]	Obesity shapes were initially constructed by principal component analysis based on datasets on 5852 obese individuals	Biomechanical model	Higher waist circumferences at identical BW increased spinal forces to the tune of ~ 20 kg additional BW and the risk of vertebral fatigue compression fracture by 3–7 times when compared with smaller waist circumferences. Spinal loads markedly increased with BW, especially at greater waist circumferences
Majumder et al. [43]	NA	Biomechanical model	Greater soft-tissue thickness over the lateral hip dissipates fall impact, and so may continue to protect against hip fracture at high body weight even when load-to-strength ratio is exceeded
Lang et al. [45]	2941 white and black women and men (aged 70–79 years)	Longitudinal	Decreased thigh muscle resulted in increased risk of hip fracture, an association that continued to be significant after further adjustment for BMD
Scott et al. [46]	1089 adults (mean ± SD age 62 ± 7 years; 51% female)	Longitudinal	Obese alone participants had significantly higher BMD at all sites compared with non-sarcopenic non-obese. Sarcopenic obese and dynapenic obese men had lower spine and total body BMD, respectively, and sarcopenic obese women had lower total hip BMD, compared with obese alone. Sarcopenic obese men had higher non-vertebral fracture rates compared to non-sarcopenic non-obese, and obese alone. Sarcopenic obese women had higher fracture rates compared with obese alone, but this was non-significant after adjustment for total hip BMD

Table 2 Obesity and vitamin D

References	Sample	Design	Results
Samuel and Borrell [51]	12,927 adults (51.1% aged 18–44; 33.0% aged 45–64; 15.9% aged 65+)	Cross-sectional	Overweight and obese individuals were 24% and 55%, respectively, less likely to have a 25-hydroxy vitamin D level of 30 ng/mL or greater compared with normal-weight individuals
Walsh et al. [52]	223 adults (aged 25–75 years in the fall and spring) 106 subjects in the winter	Cross-sectional	Serum total 25(OH)D was lower in obese and overweight subjects than in normal-weight subjects in the fall and spring but not in the winter. Bone turnover was lower, and bone density was higher, in obese people
Macdonald et al. [53]	3113 women (mean ± SD age 54.8 ± 2.3 years)	Longitudinal	Low vitamin D status is associated with greater bone turnover, bone loss, and obesity. Diet appears to attenuate the seasonal variation of vitamin D status in the early post-menopausal women at northerly latitude where quality of sunlight for production of vitamin D is diminished
Ardawi et al. [54]	1172 women (mean ± SD age 50.9 ± 12.6)	Cross-sectional	Vitamin D deficiency is highly prevalent among healthy Saudi pre- and post-menopausal women and largely attributed to obesity, poor exposure to sunlight, poor dietary vitamin D supplementation, and age
Lagunova et al. [55]	2126 adults (54% aged < 50 years; 46% aged ≥ 50 years)	Cross-sectional	The 25(OH)D level, as well as its seasonal variation and the prevalence of vitamin D deficiency, are all dependent on BMI, and age separately. The results of the study suggest that 1 in 3 women and 1 in 2 men with BMI > or = 40 are vitamin D deficient
Lagunova et al. [56]	1779 adults (mean age 48.6, range 20–79)	Cross-sectional	in patients with excess body weight, serum 1,25(OH)(2)D concentrations were associated with 25(OH)D and varied during the year
Snijder et al. [57]	453 adults (aged ≥ 65 years)	Cross-sectional	Total body fat is inversely associated with 25-OH-D levels and is positively associated with PTH levels
Hultin et al. [58]	144 adults (108 morbidly obese patients, 21 normal weighted and 15 with primary HPT (pHPT))	Cross-sectional	Obese individuals had a left-shifted Ca-PTH curve and a lower set point compared with the normal population
Vimaleswaran et al. [59]	42,024 adults (aged > 18 years)	Bi-directional Mendelian randomization analysis of multiple cohorts	A higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing BMI are likely to be small. Population-level interventions to reduce BMI are expected to decrease the prevalence of vitamin D deficiency
Chen et al. [60]	4071 adults (mean ± SD age 55.6 ± 11.1 years)	Meta-analysis of randomized controlled trials	Compared with control group, calcium supplements significantly reduced low-density lipoprotein cholesterol level by -0.12 mmol/L

Table 2 (continued)

References	Sample	Design	Results
Autier et al. [62]	800,919 adults (aged ≥ 18 years)	Systematic review of meta-analysis of prospective cohort studies and randomized clinical trials	Supplementation in elderly people (mainly women) with 20 µg vitamin D per day seemed to slightly reduce all-cause mortality. Low vitamin D status is reported in a wide range of disorders. Vitamin D supplementation leads to slight gains in survival
Shanmugalingam et al. [63]	24,731 obese adults (aged ≥ 18 years)	Systematic review of meta-analysis	There is consistent evidence for a link between obesity and cancer as well as obesity and low vitamin D. However, it seems like the significance of the mediating role of vitamin D in the biological pathways linking obesity and cancer is low
Eaton et al. [64]	2429 post-menopausal women (aged 50–79 years)	Longitudinal	Body fat distribution may play an important role in the modulation of the effect of low vitamin D concentrations on health. Although an inverse association between 25(OH)D and all-cause and selected-cause mortality was apparent, the relation was attenuated to nonsignificance when adiposity and other potential confounding factors were taken into account

such as interleukin-6 (IL-6) that may negatively interfere with the balance between bone resorption and formation [19, 22]. Osteocalcin is a molecule secreted by the osteoblasts [25]. This molecule regulates insulin secretion, insulin sensitivity, and energy expenditure [24, 25]. Insulin acts directly on osteoblasts via insulin receptors to increase the production of undercarboxylated osteocalcin, resulting in increased insulin production by the pancreas and increased insulin sensitivity. Insulin also reduces the production of osteoprotegerin (OPG), leading to increased bone resorption and subsequent decarboxylation of osteocalcin [23].

Type 2 diabetes mellitus (T2DM) is also strictly related to overweight and obesity. T2DM, in both obese and normal individuals, is characterized by higher fragility fracture risk even if is associated with higher BMD values. Indeed, the Fracture Risk Assessment Tool (FRAX) underestimates bone fracture risk in T2DM. The latter evidence might be partially explained by the increased BMD in the obese people. A practical way to adjust the risk of T2DM patients is reducing the BMD T-score by 0.5 SD when estimating the fracture risk [26, 27].

Finally, peroxisome proliferator-activated receptor gamma (PPARg) is known to be associated with the regulation of both bone mass and fat [28], increasing the commitment of pluripotent stem cells to adipocytes and inhibiting commitment to the osteoblast linage. The PPARg actions are well exemplified through their agonists, the thiazolidinediones. They decrease insulin resistance while negatively affecting bone mass and increasing the risk of fractures [28].

The obesity paradox: osteoporosis and fractures

In the past, it was generally believed that obesity was protective against fracture [29], this odd relationship has been addressed previously as one of the many aspects of the "obesity paradox" [30]. However, considering obesity as protective for bone metabolism revealed to be over-simplistic. This belief was partially suggested by the positive correlation between BMD and BMI [18, 19], and the lower incidence of hip fractures in obese subjects [31]. However, in 2011, a study from a Fracture Liaison Service in the United Kingdom reported, for the first time, an unexpectedly high prevalence of obesity (27%) in post-menopausal women presenting with a fragility fracture [32].

Indeed, most of the available evidence supports a lower risk of proximal femur and vertebral fracture in obese adults [10]. Interestingly, fracture risk in obesity is not lower at all skeletal sites; the risk of some non-spine fractures including proximal humerus (RR 1.28), upper leg (OR 1.7), and ankle fracture (OR 1.5) is higher [33, 34]. A large number of low-trauma fractures occur in

overweight and obese men and women, and the prevalence of low-trauma fractures is similar in obese and non-obese women [34]. Therefore, obesity is not entirely protective against fracture, and there are some site-specific effects on fracture.

There is a positive association between BMI and BMD [35], and these data are also confirmed by quantitative imaging methods, such as computed tomography and ultrasound. Calcaneus bone stiffness by ultrasound is greater in obesity [36] and HR-pQCT; obese adults have higher BMD, higher cortical BMD, higher trabecular BMD, and greater trabecular number at the distal radius and distal tibia [12, 37].

When dealing specifically with central adiposity, the data are not consistent. Indeed, there are reports that the larger the waist circumference of obese subjects, the less likely they are of having osteoporosis defined by DXA [38], with the association of central adiposity and bone mineral density with adiponectin levels [39], while, in other studies, visceral adiposity (assessed by waist-to-hip ratio) was significantly linked to reduced bone mass [40, 41]. Again, the relationship is complicated by many factors, since the metabolic and endocrinological status also interacts with the biomechanical influence of the load on the bone determined by the adipose tissue: in a very interesting biomechanical analysis [42], Ghezelbash et al. found that higher waist circumferences at identical body weight increased spinal forces and the risk of vertebral fatigue compression fracture by three to seven times when compared with smaller waist circumferences. In addition, spinal loads markedly increased with body weight, especially at greater waist circumferences [42].

Radius and tibia strength estimated by finite-element analysis from HR-pQCT is greater in obesity than in normal-weight controls [12]. Therefore, BMD is probably truly higher in obesity, and there is no site-specific BMD deficit to explain the site-specific fracture risk. It is possible that even if BMD increases in response to obesity, the capacity for increase is limited and eventually the load-to-strength ratio (the ratio between the load exerted on the bone and the strength withstand before fracture occurs) rises far enough to cause fracture in low-trauma injuries [43]. The increase in radius and tibia strength by HR-pQCT in obesity is proportionally less than the increase in BMI [37]. At the hip, by QCT and DXA, obese people have favourable features for bone strength, but the load-to-strength ratio is greater than normal-weight controls [16, 17]. Greater soft-tissue thickness over the lateral hip dissipates fall impact, and so may continue to protect against hip fracture at high body weight even when load-to-strength ratio is exceeded [17, 44]. Intramuscular fat content is increased in obesity, and may be associated with poorer muscle function and increased fracture risk ("dynapenic obesity", namely obesity associated with impaired muscle strength) [45–47]. Poorer muscle function could increase falls and injury when falling, and there are data showing an excess of falls in obese people [48, 49].

Thus, although BMD is higher in obesity, it may not be increased sufficiently to resist the greater forces acting when obese people fall of when are exposed to various kinds of biomechanical stressors. Non-bone factors such as muscle function and soft-tissue thickness should also be considered as contributory and protective factors (Table 1).

Obesity and vitamin D

Vitamin D is a fat-soluble vitamin and a steroid hormone that plays a central role in maintaining calcium–phosphorus and bone homeostasis, with many extra skeletal relevant implications on autoimmune diseases and improvement of glucose metabolism, muscle, and adipose tissue function [50]. Obese people have lower serum 25(OH)D than normal-weight people, and serum 25(OH)D is inversely correlated with body weight, BMI, and fat mass. This has been shown in adults and children in northern and southern Europe, Australia and New Zealand, Saudi Arabia, Latin America, and in White, Black, and Hispanic groups in the United States [51–53]. Serum 25(OH)D is about 20% lower in obese people than normal weight [51–54], and the prevalence of 25(OH)D deficiency is greater in obese people, reported at between 40 and 80% [51, 52, 55]. Other measures of vitamin D status [free 25(OH)D and 1,25(OH)2D] are also lower in obesity [52, 56]. Parathyroid hormone is often used as an indicator of vitamin D status. Parathyroid hormone (PTH) tends to be higher in obesity [57], but the relationship between serum calcium and PTH is left-shifted in obesity [58], so it is difficult to interpret the clinical significance of higher PTH. It is likely that low serum 25(OH)D is a consequence of obesity, rather than the cause of obesity. A large genetic study found that high BMI and genes that predispose to obesity decrease serum 25(OH)D, whereas low 25(OH)D and genes associated with low 25(OH)D have very little effect on obesity [59]. In meta-analysis, vitamin D supplementation has no effect on body weight or fat mass [60].

Usually, low total 25(OH)D, free 25(OH)D, and 1,25(OH)2D would lead to lower dietary calcium absorption, and increased bone turnover with lower bone mineral density (BMD). However, obese adults have lower bone turnover than normal weight, and higher BMD with thicker, denser cortices, and greater trabecular number [12]. It is important to note that in contrast, obesity in children has adverse effects on bone strength [61].

The lack of adverse effects on bone may indicate that obese people are not truly vitamin D deficient; it is possible that although serum 25(OH)D is lower (due to reduced bioavailability of cholecalciferol, sequestered by the adipose tissue), their whole-body total vitamin D stores are greater

because of the reservoir in their fat tissue, which maintains an equilibrium with serum 25(OH)D and a sufficient supply (Table 2).

An alternative explanation is that obese people are vitamin D deficient, but other effects of obesity might compensate for the negative consequences of vitamin D deficiency: for example, greater skeletal loading or the action of hormones such as leptin or oestrogen is known to have positive effects on bone mass [18, 23].

If obese people are truly vitamin D deficient, there may be implications for systems other than bone. Vitamin D deficiency has been associated with a large number of disorders, such as autoimmunity, cancer, neurodegenerative disease, and metabolic syndrome [62]. However, it should be noted that, currently, there is not yet clear evidence for a causative role of vitamin D deficiency in many of these conditions [62], as there are also other possible mechanisms than low vitamin D possibly involved in these associations, and the interaction of vitamin D and obesity in causation has not yet been clearly characterized [63].

In the US National Health and Nutrition Examination Survey population study, lowserum25(OH)D was associated with higher all-cause mortality in post-menopausal women with normal waist circumference; the hazard ratio for the lowest versus the highest serum vitamin D quartile (< 36.5 versus > 65.4 nmol/l) was 1.85 (95% confidence interval 1.00–3.44). In women with abdominal obesity, there was no association between serum 25(OH)D quartile and all-cause mortality (hazard ratio 0.96, 95% confidence interval 0.52–1.76) [64].

Conclusions

In conclusion, the data currently available and provided by many studies which compared the fracture incidence in obese versus lean subjects seem to show that obesity is associated with a higher fracture risk some sites, such as non-hip inferior limb fractures and proximal humerus, but may be protective at others (hip fractures, possibly wrist) [33]. However, it is important to note that the distribution of the BMI values may, at least to a certain extent, influence the results of these studies. For instance, when dealing with cohorts with a low prevalence of obesity, a possible increase in the fracture risk for certain sites in obese subjects may be difficult to detect. On the contrary, in cohorts with a higher prevalent of obesity, these associations may become evident.

Concerning the global risk of fracture, both the protective and harmful effects have to be considered altogether. In this way, an U-shaped curve could be hypothesized, even though the strongest data currently available concerning the influence of BMI on the risk of fracture regard subjects with low-to-very low body weight. Simply put, the higher BMD in obesity might not be sufficient to resist the greater forces involved in obese patients when the subject falls.

Fig. 1 Obesity is characterized by many features which influence the risk of fracture with counteracting effects: "the obesity paradox". On one hand, in the red circles, we have some of the negative (both metabolic and mechanical) consequences and comorbidities causing a detrimental effect on the fracture risk associated with obesity. On the other (green circles), we have a number of features which influence BMD and, therefore, the fracture risk on the opposite direction. The interaction and the degree of expression of all these features can heavily influence the fracture risk and can also be one of the main reasons for some puzzling phenomena concerning this condition. An adequate interpretation of this topic must be comprehensive of all these points (see text for further detail)

Finally, obesity can bring with itself many complications (T2DM, vitamin D deficiency, and motor disability) which, in the long run, can have a definite influence in terms of overall risk and quality of life, as well (Fig. 1).

Compliance with ethical standards

Conflict of interest The authors state that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

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