

Obesity and fracture risk

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Summary

Obesity and osteoporosis are two common diseases with an increasing prevalence and a high impact on morbidity and mortality. Obese women have always been considered protected against osteoporosis and osteoporotic fractures. However, several recent studies have challenged the widespread belief that obesity is protective against fracture and have suggested that obesity is a risk factor for certain fractures.

Fat and bone are linked by many pathways, which ultimately serve the function of providing a skeleton appropriate to the mass of adipose tissue it is carrying. Leptin, adiponectin, adipocytic estrogens and insulin/amylin are involved in this connection. However, excessive body fat, and particularly abdominal fat, produces inflammatory cytokines which may stimulate bone resorption and reduce bone strength.

This review aimed to examine the literature data on the relationships of BMI and fat mass with fractures in adult and elderly subjects. Even though the more recent studies have shown conflicting results, there is growing evidence that obesity, and particularly severe obesity, may be related to an increased risk of fracture at different skeletal sites which is partially independent from BMD.

Moreover, the relationship between obesity and fracture appears to be markedly influenced by ethnicity, gender and fat distribution.

Even though the incidence and the pathogenesis of fracture in obese individuals has not yet been clearly defined, the growing evidence that obesity may be related to an increased risk of fracture has important public health implications and emphasizes the need to develop

effective strategies to reduce fracture risk in obese subjects.

KEY WORDS: BMI; fracture; body composition; abdominal fat; obesity.

Introduction

Obesity and osteoporosis are two common diseases with an increasing prevalence and a high impact on morbidity and mortality which, during the last two decades, have become major health threats worldwide. It has been reported that age and female gender increase the risk of developing both obesity and osteoporosis. Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue leading to an increased risk of developing spontaneous and traumatic bone fractures (1). Literature data have reported that more than 40% of postmenopausal women will suffer at least one osteoporotic fracture, often leading to permanent and severe disability, impaired quality of life and even death. BMD by dual energy X-ray absorptiometry (DXA) is the most important determinant of bone strength and has been accepted as a surrogate measure for the diagnosis of osteopenia and osteoporosis.

Obesity, defined on the basis of WHO criteria as having a body mass index (BMI) ≥ 30 Kg/m², is due to an imbalance in which energy intake exceeds energy expenditure over a prolonged period, with an excessive body fat accumulation to a degree that adversely affects health (2). Body weight has been reported to be influenced by several environmental, nutritional and hormonal factors. Moreover, obese subjects present an increased risk of being affected by type II diabetes, hypertension, cardiovascular diseases and some cancers. However, for many years body weight has been considered one of the important determinants of BMD and a positive relationship between body weight or BMI and BMD has been reported (3, 4). An inverse relationship between body weight or BMI and the risk of any fractures has also been shown (5). In particular, obese women have always been considered protected against osteoporosis and osteoporotic fractures. However, in recent years the association between obesity and osteoporosis has been actively investigated from epidemiological, clinical and basic research points of view, making evident that osteoporosis and obesity can no longer be considered antithetic, whereas they are closely connected and may present common pathophysiological mechanisms.

Relationships of fat mass with bone mass and bone metabolism

Body weight is generally considered a strong predictor of bone mass in both males and females. In fact, extensive epidemiological studies have reported that elevated body

weight or body mass index are positively correlated with increased bone mineral density and with reduced risk of fragility fractures. The generally accepted explanation of this relationship is that a larger body mass induces greater mechanical loading on bone, with a consequent increase in BMD to accommodate the greater load (5, 6).

Many studies have reported that in healthy premenopausal and postmenopausal women total body fat is positively related to bone mineral density, which is commonly considered the most important measurable determinant of fracture risk, and that decreased body weight leads to bone loss. On this basis low body weight has been incorporated into the FRAX and Garvan algorithms, calculations aimed to predict an individual's prospective fracture risk. In recent years there has been a growing interest in studying the influence of body composition on bone status and in particular the relationship between fat mass and bone mineral density.

Abundant adipose tissue is considered an important source of estrogen production and may contribute to increased BMD; however, this finding has been confirmed in women but not in men (7). Also, Reid did not find significant relationships between fat mass and BMD in men (8). These inconsistent findings suggest that the impact of fat mass on bone may be mediated by several factors independent of mechanical stimulation. Recently, some studies, mainly by Chinese Authors, have contributed to clarify these points. In a large-scale sample of Chinese and Caucasian subjects Zhao et al. (9) found that there is a positive correlation between fat mass and bone mass in both sexes, when results are not corrected for the mechanical loading effect of body weight. However, when the mechanical loading effect caused by total body weight is statistically removed, both fat mass and percentage fat are negatively correlated with bone mass (9). Consistent with this finding two more recent studies, carried out on large cohorts of Chinese and Korean subjects, found that subjects with a higher percentage of body fat presented lower bone mineral density and a higher prevalence of osteoporosis (10, 11).

However, the relative effect of lean mass and fat mass, the major components of body weight, on BMD still remains controversial. Some studies suggest that in postmenopausal women, the effect of fat mass on BMD is more important than that of lean mass. Opposite results have also been reported showing that lean mass, not fat mass, is more closely associated with BMD. Still other studies have found that both lean mass and fat mass were significant predictors of BMD, with lean mass being a more important predictor than fat mass in premenopausal women, and fat mass more important than lean mass in postmenopausal women (3, 12-14). Moreover, Gnudi et al. (15) found that the relationship between BMD and body composition is different between women with or without osteoporosis. In fact, in osteoporotic women lean mass and fat mass were significantly associated with BMD, whereas in women without osteoporosis only lean mass was significantly associated with BMD (15). Similarly, Cui et al. observed that in postmenopausal women fat mass was positively associated with BMD at all sites, whereas both lean mass and fat mass contributed to hip BMD (16). In a recent study carried out in 1034 elderly Italian men and women aged 60 years or over we have reported that, both in elderly men and postmenopausal women lean mass and fat mass are positively associated with BMD, but with relevant difference according to the differing skeletal sites and genders; the role of lean mass being more important in males,

whereas in women the role of fat mass prevails (17). Therefore, the above mentioned studies suggest that the relationships of fat mass and lean mass with BMD are influenced by gender. Although several hypotheses have been made to explain the influence of lean mass on bone, the more commonly accepted explanation is that increased muscular strain can induce periosteal apposition, which can also be stimulated directly by the action of mechanical strain on mechanoreceptors in osteocytes. Moreover, according to space flight and bed-rest studies, lean mass may contribute to an increase in BMD by causing increased mechanical loading (18). The major mechanisms by which fat mass may influence bone tissue have recently been reviewed by Reid and are listed in Table 1 (18). Firstly, an increased fat mass imposes a greater mechanical stress on bones, and in response bone mass increases to accommodate the greater load. Moreover, many hormones may link fat mass to bone tissue. An excess in fat mass is associated with an increased aromatization of androgens to estrogens in adipose tissue, an increased secretion of insulin and amylin from pancreatic β -cells, decreased sex hormone binding globulin serum levels with increased levels of free sex steroids and changes in the production of adipokynes, among them the more studied being leptin and adiponectin. Leptin, the most widely recognized adipocyte-derived hormone, is mainly known for its function of suppressing appetite and increasing energy expenditure, and is considered to play a crucial role in the protective effect of fat on bone. However, in vitro studies have recently confirmed that the effect of leptin on bone is complex and not completely understood (19). Moreover, some cross sectional studies to assess the role of leptin on BMD have reported both negative and positive effects (20, 21).

Adiponectin, an adipocyte-produced hormone that correlates negatively with obesity in general and central adiposity in particular, has been reported to stimulate both bone formation and bone resorption but its effect on BMD remains controversial (20, 22-24). At present, no accepted explanations exist in literature about the negative effect of an excessive body fat mass or fat percentage on BMD reported by several Authors (9-11). The possible mechanism may be represented by the fact that obesity is now known as a systemic inflammatory condition and obese tissue secretes various inflammatory cytokines (mainly IL-6 and TNF- α) which may up-regulate the receptor activator of nuclear factor κ

Table 1 - Mechanism by which obesity influence bone status.

A - Positive signals (\uparrow BMD)
▪ Mechanical load
▪ Conversion of androgen to estrogen
▪ Increased levels of free sex-hormones
▪ Secretion of insulin and amylin by β -cells
▪ Increased glucagon-like peptide-2
▪ Leptin (?)
▪ Adiponectin (?)
B - Negative signals (\downarrow BMD)
▪ Proinflammatory cytokines (IL-6, TNF- α)
▪ Leptin (?)
▪ Adiponectin (?)
▪ Reduced 25OHD levels
▪ Increased PTH levels

ligands, stimulating osteoclastogenesis and leading to bone resorption. Moreover, it has been reported that the production of pro-inflammatory cytokines (IL-6 and TNF- α) is higher in abdominal fat than in subcutaneous fat, whereas aromatase activity and adiponectin secretion are lower in visceral fat (25, 26).

Relationships of BMI and body fat with fractures

Many epidemiological studies have reported that low body weight and low BMI are risk factors for fragility fracture. In particular, the results of a meta-analysis of 60,000 men and women from 12 prospective, population based cohorts showed that total fractures, osteoporotic fractures and hip fractures were all inversely correlated to BMI in both men and women (5). Moreover, these associations were lost after adjustment for BMD, suggesting that the protective effect of BMI is mediated through its effect on BMD. However, for hip fracture there was a component of BMI protective effect which was independent from BMD, probably due to the shock-absorbing effect of adipose tissue over the greater trochanter (5).

In the Study of Osteoporotic Fractures, both lean mass and fat mass were shown to be related to hip fracture risk; in fact, the subjects in the lowest quartiles of either fat mass or lean mass presented an increased risk of hip fracture (27). Moreover, in the study by Schött (28) carried out on a large population of nearly 8,000 French women over the age of 75 years there was a 40% increase in hip fracture risk for each standard deviation decrease in fat mass, but no effect of lean mass.

However, several recent studies have challenged the widespread belief that obesity is protective against fracture and have suggested that obesity is a risk factor for certain types of fracture. In particular, the study by Hsu (10), carried out in a large cohort of Chinese men and women, showed that non-spine fractures were significantly higher in subjects with a higher percentage of body fat, independent of body weight. In the study by Hsu there were significant and independent linear trends for higher ORs of self-reported non-spine fractures in men and premenopausal women with higher percentage of fat mass but not in postmenopausal women (10). The study by Premaor et al. (29) evaluated 1,005 postmenopausal women younger than 75 years of age presenting to a Fracture Liaison Service in Cambridge (U.K.) with a low trauma fracture, and reported that 27.7 % of women presenting with a fracture had a BMI ≥ 30 Kg/m². This study also reported that fractures of the wrist were significantly less common and hip fractures significantly more common in obese than in non-obese women.

The Global Longitudinal study of Osteoporosis in Women (GLOW), a prospective cohort study involving 723 physician practices in 10 countries, has reported that fractures in obese women accounted for 23% and 22% of all previous and incident fractures, respectively (30). Moreover, the risk of incident ankle and upper leg fractures was significantly higher in obese than non-obese women, while the risk of wrist fracture was significantly lower. On the other hand obese women with fracture tended to have higher rates of comorbidities than others (especially self-reported asthma and emphysema) (30).

A previous Italian study, carried out on 2,235 Italian postmenopausal women with fracture, reported that increased

BMI was associated with a significantly higher risk of humerus fracture and a lower risk of hip fracture, but no relationship was seen between BMI and either wrist or ankle fractures (31).

Using data from the Womens' Health Initiative (WHI) study in postmenopausal women, Beck and colleagues reported a significantly greater incidence of lower-extremity fractures in obese versus normal weight women and a significantly lower incidence of hip fractures (32).

Another recent study by Prieto-Alhambra et al. (33) carried out on a very large Spanish population of women aged 50 years or over has confirmed that the association between obesity and fracture in postmenopausal women is site-dependent, obesity being protective against hip and pelvis fractures but associated with an almost 20% increase in risk for proximal humerus fracture compared with normal/underweight women.

Data on vertebral fractures in obese subjects are scarce although in an Italian study carried out on a small cohort of postmenopausal women higher BMI appeared to be associated with a higher likelihood of having vertebral fractures, irrespective of the positive association between weight and BMD (34).

In a study of men and women aged 20-80 years Bergkvist et al. reported that ankle fracture was significantly related to obesity (35). Recently, a prospective study by the Osteoporotic Fractures in Man Study (MrOs) Research Group has reported that obesity was associated with an increased risk of non-spine fractures in men aged 65 years or over, but the association was no longer significant after adjustment for mobility limitations (36). In this latter study the risk of hip fractures was higher in men with more severe obesity (BMI ≥ 35 Kg/m²), an effect that was independent of BMD and mobility (36).

This latter finding contrasts with a reduced risk of hip fracture in obese postmenopausal women reported by several studies (31, 33) possibly reflecting a different distribution of fat in obese men and women (37).

Moreover, a recent prospective study of the EPIC cohort reported that higher body fat mass is associated with lower risk of hip fracture amongst women but not men (38). In contrast a study carried out in Korean postmenopausal women reported that high percentage body fat and waist circumference were associated to an increased risk of vertebral fractures (11). However, the results of this latter study (11) were not adjusted for BMD, a major determinant of fracture risk. A recent study carried out in 1,011 male and female participants in the Tasmanian Older Adult Cohort study has reported a positive association between prevalent thoracic vertebral fractures and BMI, total fat mass and waist circumference, while there was a negative relationship between prevalent thoracic vertebral deformities and total fat mass in men (39). In this latter study there were no statistically significant associations between BMI or body fat and vertebral fractures at lumbar spine in either men or women. In addition, the number of vertebral deformities increased as BMI or fat mass increased in women but decreased with increasing total fat mass in men. Moreover, in women associations between fat mass and vertebral deformities were mainly linear, but there was evidence of a threshold effect in women with a BMI > 35 Kg/m² (39).

Table 2 shows the characteristics of recent studies on the relationship between obesity and fracture.

At present, despite the increasing amount of literature data

Table 2 - Obesity and fracture: results of more recent studies.

References	Country	Population	Assessment of obesity	Increased fractures	Reduced fractures	Study
Women						
Compston J et al. [30]	U.K.	60393 women ≥55yrs	BMI	Upper leg; ankle	Wrist	Longitudinal
Premaor MO et al. [29]	U.K.	1005 women ≥75yrs	BMI	Hip	Wrist	Cross-sectional
Gnudi S et al. [31]	Italy	2235 PM women	BMI	Humerus	Hip	Cross-sectional
Beck JJ et al. [32]	USA	78013 women aged 50-79yrs	BMI	Lower extremity	Hip; vertebrae	Longitudinal
Prieto-Alhambra D et al. [33]	Spain	832775 women ≥50yrs	BMI	Humerus	Hip; pelvis	Cross-sectional
Pirro M et al. [34]	Italy	362 PM women	BMI	Vertebrae	-----	Cross-sectional
Bergkvist D et al. [35]	Sweden	79 women aged 27-49yrs	BMI	Ankle	-----	Cross-sectional
Moayyeri A et al [38]	U.K.	8319 women aged 42-82yrs	% body fat	-----	Hip	Longitudinal
Kim KC et al. [11]	Korea	907 women aged 50-80yrs	% body fat, Waist circumference	Vertebrae	-----	Cross-sectional
Laslett LL et al. [39]	Australia	522 women aged 50-80yrs	BMI, total fat, waist circumference	Vertebrae	-----	Cross-sectional
Hsu YH et al. [10]	Chine	2248 women aged 25-64yrs	% body fat	-----	-----	Cross-sectional
Men						
Nielson CM et al. [36]	USA	5995 men ≥ 65yrs	BMI	Hip; Non-spine	-----	Longitudinal
Moayyeri A et al [38]	U.K.	6470 men aged 42-82yrs	% body fat (BIA)	-----	-----	Longitudinal
Laslett LL et al. [39]	Australia	489 men aged 50-80yrs	BMI, total fat, waist circumference	-----	Vertebral	Cross-sectional
Hsu YH et al. [10]	Chine	7137 men aged 25-64yrs	% body fat	Non-spine	-----	Cross-sectional

available, most questions remain unanswered. Increased risk of falls and reduced physical function have been demonstrated in obese men and women. Moreover, it has been reported that obese subjects with fracture present several markers of frailty, and that in these subjects higher BMI is significantly associated with a number of comorbidities including asthma, emphysema and type II diabetes (30).

Furthermore, although greater soft tissue padding may reduce skeletal trauma following a fall, poorer protective responses to falling and the higher impact of the fall owing to high body weight may offset this potential benefit. In addition, the risk of falling may be increased in obese subjects as a result of reduced muscular strength and mobility (29, 40, 41).

Instead the reasons for site specific differences in fracture site in obese compared with non-obese individuals have not been established. However, it is consistently found that obesity is associated with reduced levels of 25-hydroxyvitamin D and that fat mass and 25-hydroxyvitamin D serum levels are inversely related probably for the sequestration of this fat soluble vitamin in adipose tissue. In addition, the consequent higher serum parathyroid hormone levels reported in obese individuals could have an adverse effect on cortical bone (42, 43).

Although some previous studies, generally carried out in Asian populations have suggested an inverse association between visceral adipose tissue and BMD (11, 44), the literature data regarding the impact of body fat mass distribution on BMD and fracture risk still remains controversial. In fact, the possible negative association between central obesity and fracture risk may be supported by the fact that in the

Rancho Bernardo Study, after adjusting for BMI, the presence of metabolic syndrome was associated with lower BMD and an higher incidence of osteoporotic non vertebral fractures (45). Moreover, another study carried out on a Scandinavian population has yielded opposite findings reporting a protective effect of abdominal fat on BMD (46). In a recent study we have reported that in men android fat is positively associated with BMD at different skeletal sites, whereas in women BMD at the same skeletal sites is negatively associated with gynoid fat (17). Indeed, literature data regarding the impact of regional fat distribution on BMD still remains controversial; the uncertainty of literature being due to the fact that the majority of studies were carried out using DXA technique which is not able to precisely distinguish between subcutaneous and visceral fat. The fact that most of the previously mentioned studies have been conducted on women of oriental origin may contribute to the uncertainty of literature data. In particular, it has been reported that for the same BMI Asians had higher body fat percentage and abdominal obesity components compared with those of Caucasian subjects and this may be deleterious for bone (47). In fact, it has been reported that the production of pro-inflammatory cytokines (IL-6 and TNF- α is higher in abdominal fat than in subcutaneous fat, whereas aromatase activity and adiponectin secretion is lower in visceral fat (25, 26).

Conclusions

Even though the incidence and the pathogenesis of fracture in obese individuals has not yet been clearly defined, the

growing evidence that obesity may be related to an increased risk of fracture has important public health implications. In fact, due to the rapidly rising incidence of obesity and the greater risk of non-union and postoperative complications in obese patients with fracture, the economic burden of fractures in obese subjects is expected to markedly increase over the coming years. This emphasizes the need to develop effective strategies to reduce fracture risk in obese subjects.

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