

# Obesity and fractures

## *Obesidade e fraturas*

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### ABSTRACT

Until recently obesity was believed to be protective against fractures. However, a report from a Fracture Liaison Clinic in the UK (2010) reported a surprisingly high proportion of obese postmenopausal women attending the clinic with fractures, and in the GLOW study (2011), a similar prevalence and incidence of fractures in obese and non-obese postmenopausal women was observed. Subsequently, other studies have demonstrated the importance of obesity in the epidemiology of fractures. Obese women are at increased risk of fracture in ankle, leg, humerus, and vertebral column and at lower risk of wrist, hip and pelvis fracture when compared to non-obese women. In men, it has been reported that multiple rib fractures are associated with obesity. Furthermore, falls appear to play an important role in the pathogenesis of fractures in obese subjects. Regarding hip fracture and major fractures, the FRAX algorithm has proven to be a useful predictor in obese individuals. Obese people are less likely to receive bone protective treatment; they have a longer hospital stay and a lower quality of life both before and after fracture. Moreover, the efficacy of antiresorptive therapies is not well established in obese people. The latter is a field for future research. *Arq Bras Endocrinol Metab.* 2014;58(5):470-7

### Keywords

Obesity; fractures; osteoporosis; osteopenia

### RESUMO

Acreditava-se que pessoas obesas estavam protegidas contra fraturas. No entanto, um estudo realizado no Reino Unido (2010) encontrou uma proporção surpreendentemente alta de obesidade entre as mulheres na pós-menopausa que se consultaram em uma Clínica de Fraturas Ósseas. Da mesma maneira, o estudo GLOW (2011) observou prevalência e incidência semelhantes de fraturas em mulheres na pós-menopausa obesas e não obesas. Posteriormente, vários outros estudos têm demonstrado a importância da obesidade na epidemiologia de fraturas. Mulheres obesas têm maior risco de fratura no tornozelo, na perna, no úmero e na coluna vertebral e têm menor risco de fratura de punho, quadril e pelve quando comparadas às mulheres não obesas. A associação entre fraturas múltiplas de costelas e obesidade foi descrita em homens. Além disso, as quedas parecem desempenhar um papel importante na patogênese de fraturas em pacientes obesos. O algoritmo FRAX parece ser uma ferramenta útil na predição do risco de fraturas em indivíduos obesos. Indivíduos obesos são menos propensos a receber tratamento preventivo para as fraturas ósseas e, quando sofrem uma fratura óssea, sua internação costuma ser mais longa do que a internação de indivíduos magros. A qualidade de vida dos indivíduos obesos é menor antes e depois da fratura. Não obstante, a eficácia de terapias antirreabsorção não está bem estabelecida em pessoas obesas. Este último é um campo para pesquisas futuras. *Arq Bras Endocrinol Metab.* 2014;58(5):470-7

### Descritores

Obesidade; fraturas ósseas; osteoporose, osteopenia

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## INTRODUCTION

Obesity and bone fractures are common disorders associated with high morbi-mortality and elevated public health costs worldwide (1-3).

Until recently, it was generally believed that obesity was protective against fracture. This misconception was in part conceived from the positive correlation between bone mineral density (BMD) and body mass index

(BMI) (4,5), and the lower incidence of hip fractures in obese subjects (6). In 2010, a study from a Fracture Liaison Service in the United Kingdom reported for the first time an unexpectedly high prevalence of obesity (27%) in postmenopausal women presenting with a fragility fracture (7).

Confirmation that obesity was not a protective factor against low trauma fractures was reported in 2011, when results of the Global Study of Osteoporosis in Women (GLOW) were presented (8). This multicentre prospective observational study, conducted in 60,393 postmenopausal women, showed a comparable prevalence and incidence of fractures in normal weight and obese women (8).

Subsequently, other investigators have studied the impact of obesity on bone mass and the risk of fracture (9-14). The present review focuses on the epidemiology, risk factors, diagnosis, and management of fractures in obese postmenopausal women and older men.

## **FRACTURE EPIDEMIOLOGY – OBESITY IS NOT PROTECTIVE**

Evidence from the literature supported the initial findings of the Fracture Liaison Service study from Cambridge UK (7). Ong and cols. evaluated 4,288 men and women who attended the Fracture Liaison Service of East Midlands Trauma Centre in Nottingham, UK and found a prevalence of obesity of 30% (15). As previously mentioned, in the GLOW study no statistically significant differences were seen in occurrence of fractures in obese and non-obese individuals, respectively 22.2% *versus* 22.7% for prevalence and 6.2% *versus* 6.6% for incidence (8).

Interestingly, obese men are not protected against hip fracture, as is seen in women. The Multicentre Osteoporotic Fracture in Men Study (MrOS), conducted in the USA, included 5,995 males aged 65 years or more, and found that a higher BMI was associated with increased fracture risk (16). In this study, 62% of hip fractures and 68% of non-vertebral fractures were seen in overweight and obese men (16). Similarly, analysis of the National Health and Nutrition Examination Survey I (NHANES) in 2012, reported that obesity was present in 58% of men with fracture (10). In the North American multicentre Study of Osteoporotic Fractures (SOF), which followed 7,978 women aged 65 or more years of age for 11.3 years, the incidence of non-vertebral fractures was 37.5% in obese women versus 44.3% in non-obese women (17).

In the Million Women Study, in which 925,345 women from the UK were followed for 6.2 years or longer to assess the effects of hormone replacement therapy on diverse endpoints, the incidence of hip fractures in obese and overweight individuals was also remarkable. Thus, despite the inverse correlation of weight and fractures observed, a high proportion (40%) of women with hip fracture were overweight or obese (18). These results are in agreement with the aforementioned analysis of NHANES, which demonstrated that 46% of hip fractures occurred in women who were obese or overweight (10).

Results from meta-analysis have been used to describe the relationship between bone density and BMI. De Laet and cols. identified an inverse relation (non-linear) between BMD and incidence of fractures (19). They observed a higher risk of fractures in subjects with BMI under 20 kg/m<sup>2</sup> but only small increments above BMI of 25 kg/m<sup>2</sup> (19). Interestingly, in the same study the relationship between BMI and non-hip fractures disappeared (19). Complementary data came from the work of Johansson and cols. including 398,610 women from 25 prospective studies (80% which were population-based) (20). This study found a small, but progressive risk for fractures after adjustment for BMD. In this meta-analysis, an increase of 1 kg/m<sup>2</sup> above a BMI of 25 kg/m<sup>2</sup> corresponded to an increase of 1% in the risk of fracture [HR 1.01 (95%CI 1.01,1.02)] (20).

## **SITE OF FRACTURE**

Several studies have demonstrated that the relationship between BMI and fracture is site-specific (8,11,12,14,16,21,22). While obesity is protective against hip fracture in women, it is associated with higher risk of fractures at some other sites. One reason for the lower frequency of hip fracture may be related to the presence of fat tissue (padding) surrounding the pelvis and the femur that reduces the impact of falling (23). On the other hand, obese subjects are at higher risk of falling and less well able to protect themselves against a fall (24-26). Falls in individuals who are overweight or obese are more likely to occur backwards or sideways, in contrast to forward falls in leaner individuals (27). Exaggeration of inversion and eversion of the ankle and lower leg in obese subjects may be also responsible for a higher prevalence of fractures at these sites. Moreover, increased body weight can also promote an increase in the pressure (stress) in some sites, predisposing to fracture (28).

The commonest sites of fractures in obese subjects are shown in table 1. As can be seen, obese women experience more fractures in the ankle, leg, humerus, and vertebral column and fewer in the wrist, hip and pelvis. In men, it has been reported that multiple rib fractures are associated with obesity. In a population based-study in Spain, analysing 139,419 men aged 65 years or over, hip fractures in obese individuals were significantly less common than in non-obese men (11). These data are in contrast to those of Nielson and cols., who found an increased incidence of hip fracture in men after adjustment for BMD (16).

**Table 1.** Fracture sites and their association with obesity in women and men

Fracture site	Obese women	Obese men
Ankle	Positively associated (64,65)	Positively associated (16,65)
Lower leg	Positively associated (66)	Positively associated (16)
Upper leg	Positively associated (8,66)	–
Proximal humerus	Positively associated (12,22)	Null (11)
Multiple rib	Null (12)	Positively associated (11)
Vertebral	Positively associated (9,13,14,67)	Negatively associated (11)
Wrist	Negatively associated (17)	Negatively associated (11)
Hip	Negatively associated (12)	Positively associated after adjust for BMD (16)*
Pelvis	Negatively associated (12)	Negatively associated (11)

\* Negatively associated with hip fractures without BMD correction (11); however, in the MrOS study hip fracture was positively associated with obesity after BMD adjustments (16).

## RISK FACTORS FOR FRACTURE

Obese and non-obese individuals share similar risk factors for fractures. Thus, age, history of previous fracture, family history of fracture (maternal), and use of glucocorticoids increase the risk of fractures in obese women (8). In addition to this, falls play an important role in obese individuals as does reduced physical mobility (8,16).

Obesity-associated comorbidities such as diabetes (Table 2) that also predispose to fractures have been identified as risk factors for fractures in obese women (8). The association of fractures with poor or fair general health and co-morbidities in women (8) and with the narrow walk pace (16) in men also suggests that, these individuals share some aspects of the frailty of elderly people.

The progressive increment of BMD with BMI is well established; however it might be not strong enough to compensate for the increased mechanical stresses on the skeleton. Premaor and cols. investigated the relationship between BMD and fractures in obese women (17). In this study, the risk of non-vertebral fractures increased 60% for each corresponding reduction of one standard deviation (SD) of BMD in the femoral neck (FN). Moreover, overweight or obese women with fractures had a mean FN BMD T-score of -1.5 (CI95% 1.4, 1.6), suggesting that fractures occurred at a higher BMD than in lean women (17).

The risk factors of fractures in obese people are described at table 2.

**Table 2.** Risk factors associated with fractures in obese subjects (8,16,17)

Risk factor	
Reported in women	Reported in men
Age	
Previous fracture	Previous fracture
Maternal hip fracture	
Low BMD*	
Use of arms to assist stand from a sitting position	Mobility limitations Difficulty climbing 10 steps Difficulty walking two blocks
Falls	
Two or more in the previous year	
Poor or fair general health	Narrow walk pace
Glucocorticoid use	
Comorbidities	
Asthma	
Emphysema	
Diabetes with insulin use	

\* OR 1.6 (CI 95% 1.5, 1.8) per 1 SD decrease at femoral neck (17).

## FRACTURE RISK ASSESSMENT

The World Health Organization (WHO) supports the estimation of fracture probability using the FRAX® algorithm (29). This tool defines the 10-year probability for hip or other major fracture (clinical vertebral, forearm, hip and humerus) in an individual and it is freely available on the web (<http://www.shef.ac.uk/FRAX/>). Because BMD and BMI are included in the algorithm, its applicability to obese individuals might be questioned (30,31).

It is important to emphasize that changes in the amount and distribution of body fat are likely to affect both accuracy and precision of BMD (32). However, it

is not known how much of this error would affect the interpretation of the DXA results. Studies that assess the real effect of fat on the BMD measured by DXA are difficult to conduct. When lard was placed above the hip and the spine of lean subjects, there was a small increase in BMD at the hip (1.6%) and a small decrease in BMD at the spine (0.7%) (33). In a recent paper, Yu and cols. demonstrated that quantitative computed tomography (QCT) was superior to DXA in the evaluation of bone mass in obese subjects after bariatric surgery (34). In the latter, the correlation between the two methods was only moderate and BMD measurements at hip were overestimated by DXA (34).

The ability of FRAX to predict fractures in obese postmenopausal women was addressed in a recent study (35). In spite of a lower estimated probability of fractures in obese than in non-obese women with fracture, the accuracy of FRAX was similar in both groups. In addition, in the same study, the net benefit (analysis that balances the false positives and false negatives employing a decision curve using clinical practice models) had a satisfactory performance in both obese and non-obese women (35). For hip fractures, FRAX scores which included BMD in obese subjects were superior to FRAX scores without BMD (35). It is important to note that FRAX, although useful in obese women, has not been adequately studied in situations where the BMI surpasses 40 kg/m<sup>2</sup> and the Internet tool of FRAX accepts the insertion of a maximum weight of 125 kg for calculation of the risk of fracture.

## BONE AND FAT CROSSTALK

Although the association between obesity and fractures appears to be a paradox at first sight, there has been some progress in the understanding of the crosstalk between the bone tissue and the adipose tissue. The apparent ambiguity may be partly linked to the well-documented relationships between oestrogens and obesity. Obese post-menopausal women tend to have higher serum levels of oestrogen than lean post-menopausal women (4,5). These findings explain in part the high bone mass found in association with higher BMI. Nevertheless, oestrogen is not the only factor regulating bone mass and several factors may affect both bone and fat mass: both adipose tissue and bone cells produce factors that affect each other.

Adiponectin is a molecule produced by adipocytes that appears to have a deleterious effect on bone (5,28).

Although adiponectin is inversely related to BMI, it appears to be a marker of a disrupted adaptive response in overweight subjects (5,28). In the Health Aging and Body Composition Study, serum levels of adiponectin were significantly higher in overweight women with fractures when compared with overweight women without fractures (36). Another important factor is leptin which interferes with bone metabolism through complex mechanisms (36,37). Leptin appears to act by two seemingly contradictory mechanisms. Individuals with high serum levels of leptin have increased bone mineral density as measured by DXA (36). 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 (37). Moreover, adipose tissue also produces inflammatory cytokines, such as interleukin 6 (IL6) that may negatively interfere with the balance between bone resorption and formation (5,28).

Osteocalcin is a molecule secreted by the osteoblasts (38). This hormone regulates insulin secretion, insulin sensitivity and energy expenditure (37,38). 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 (38).

Finally, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) is known to be associated with the regulation of both bone mass and fat (39), increasing the commitment of pluripotent stem to adipocytes and inhibiting commitment to the osteoblast lineage. The PPAR $\gamma$  actions are well exemplified through their agonists, the thiazolidinediones. They decrease insulin resistance while negatively affecting bone mass and increasing the risk of fractures (39).

## MANAGEMENT

One key question regarding the management of obese individuals and fractures is whether weight reduction may be beneficial. Although a reduction in BMI improves many clinical outcomes in obesity, weight loss has been associated with an increase in fractures in men and women (40-42). Thus, both voluntary and involuntary weight reduction is associated with increased risk (43). It is still uncertain whether supplementa-

tion of calcium, vitamin D, proteins and other nutrients during a restriction diet can prevent loss of bone mass, given the heterogeneity of many different studies including only a small number of patients, short time duration and several endpoints (including substitutes as BMD). A concomitant physical exercise program may attenuate bone loss during caloric restriction (44,45); however, no study has adequately analysed the impact of exercise and diet on the incidence of fractures (46).

Although non-pharmacological measures such as cessation of smoking, avoidance of alcohol excess, and regular weight bearing exercises have not been evaluated for their impact on fractures, they should be advised by the doctor. It is particularly important to perform assessment of the risk of falls and institute preventive measures where appropriate: as discussed previously in this review, falls play an important role in the development of fractures in obese subjects.

Currently, vitamin D is the only drug recognized to reduce the risk of falls (47) and supplementation of this vitamin may be beneficial given the reports of lower serum 25-hydroxyvitamin D in obese persons, in whom higher doses are often required to achieve adequate serum levels of 25-hydroxyvitamin D (48).

It is not known if pharmacological therapy is effective in reducing fractures in obese individuals. The majority of clinical trials that evaluated the efficacy of these drugs in fracture prevention included only a small number of obese subjects and most of those included had a low BMD, limiting the ability to extrapolate results to most obese individuals. Another important issue regarding pharmacotherapy in obese individuals is the higher number of patients with fracture who are not treated in comparison to those who are not overweight. In the GLOW study, only 27% of obese women with incident fracture received bone protective therapy, a minor proportion compared with non-obese (41%) (8). Factors contributing to non-treatment may be related to the perception that fractures in obese are not related to bone frailty as well as the uncertainties regarding the efficacy of drug therapy.

A greater reduction in vertebral fractures in women with BMI  $\geq 25$  kg/m<sup>2</sup> than in women with BMI  $< 25$  kg/m<sup>2</sup> was reported with the use of annual infusions of 5 mg of zoledronic acid in the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) study (49). In this study, postmenopausal women were followed for 3 years; no differences were observed between obese and overweight/

obese women in non-vertebral fracture reduction (49). Another bisphosphonate, clodronate, was shown to decrease non-vertebral fractures in postmenopausal women not selected on the basis of fracture and BMD (50). The reduction of these fractures varied according to BMI as follows: BMI  $\leq 21$  kg/m<sup>2</sup> – 40% [HR 0.60 (95%CI 0.45, 0.81)], BMI  $\geq 26$  kg/m<sup>2</sup> to  $< 30$  kg/m<sup>2</sup> – 25% [HR 0.75 (95%CI 0.62, 0.92)], and BMI  $\geq 30$  kg/m<sup>2</sup> – 10% [HR 0.90 (95%CI 0.69, 1.17)] (50). Finally, denosumab was effective in reducing the incidence of vertebral fractures regardless of BMI, although a sub-group analysis of this study – Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM), did not demonstrate significant protection against non-vertebral fractures in overweight or obese women (51).

## FRACTURE MORBIDITY AND MORTALITY IN OBESE INDIVIDUALS

Studies that have evaluated the recovery of obese individuals after fracture demonstrated an increased morbidity. Thus, obese subjects experienced a higher prevalence of co-morbidities, increased risk of non-union of fractures, more post-operative complications and longer time for recovery (52-56). However, these studies included both low-impact and high-impact fractures.

In the GLOW study, obese women with fractures had a longer hospital stay than non-obese women, even after adjustments for age, co-morbidities and type of fractures (median, 6 vs. 5 days;  $p = 0.017$ ) (21). In the same study, the physical function and vitality were assessed through the quality of life questionnaires SF-36 and EuroQol EQ-5D tool. The obtained scores were worse in obese than non-obese woman before and after fracture (21).

There is a lack of data regarding mortality of obese individuals after low-impact bone fractures. Analyzing the population health database from the family strategy program SIDIAP® (Catalunya, Spain), Prieto-Alhambra and cols., described longer survival of overweight and obese individuals than normal weight subjects (18.5 to  $< 25$  kg/m<sup>2</sup>) after incident clinical fracture (57). This observation is consistent with other reports of the “obesity paradox” in conditions such as congestive cardiac failure, chronic renal insufficiency and chronic obstructive pulmonary disease (58-61). The theory behind this *obesity paradox* is that some harmful risk factors such as obesity are not deleterious in specific conditions (*e.g.*

elderly subjects or individuals with chronic diseases) but are associated with better survival. Obesity seemed not to be deleterious in a population cohort of Olmsted Country (Minnesota, US), where the risk of cardiac and non-cardiac post-operative complications was similar among overweight, obese patients and subjects within the normal weight range (62,63).

## CONCLUSION

The proportion of fractures occurring in obese people is considerable, and is likely to increase with the progressive rise in obesity in the world population. Subjects with higher BMI are at higher risk of fractures at some sites such as the humerus, lower leg and ankle. This may be at least in part related to the increased risk of falls and their different pattern when compared to non-obese individuals. Clinical risk factors for fracture are similar in obese and non-obese subjects. Although fractures in the obese population occur at a higher BMD than in non-obese subjects, the inclusion of BMD in the algorithm FRAX is superior to FRAX without the inclusion of BMD in the prediction of hip fractures in obese individuals. For major osteoporotic fracture prediction, the FRAX tool may be used with or without BMD.

Mortality in obese people after fracture is less than that of normal weight subjects with fracture although longer hospitalization after fracture and lower quality of life in these individuals both before and after fracture have been documented. Of note, the proportion of obese subjects undergoing preventive treatment for fractures is low, and inferior to that in the non-obese. The reasons for these differences should be established in further studies; in addition, the efficacy of bone protective therapy in obese individuals remains to be established.

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