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Obesity and Fractures: Between Black and White Aspects

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Abstract

Obesity, a worldwide medical problem, associates a large panel of disorders but traditionally osteoporosis was not considered one of them. This mini-review targets human and animal studies related to this topic. DXA is the golden standard of fracture risk assessment by providing Bone Mineral Density (BMD) which is directly correlated to Body Mass Index (BMI). Recent studies found that the correlation become weaker at BMI >30 kg/sqm while associating a higher mechanical load. The obesity-related fracture risk includes a blunt bone turnover markers status and a pro-inflammatory environment as IL-6, TNF-α. Common pathogenic pathways involve both the skeleton and the metabolic complications of obesity as growth hormone, insulin-like growth factor-1, angiotensin II and ghrelin. On the contrary, estrogens are fat-derived by aromatase conversion being bone protective as androgens or insulin resistance. Leptin and adiponectin are produced by adipose tissue playing multiple roles including on bone cells. The overlapping factors in obese persons that elevate the fracture risk are the vitamin D deficiency and sarcopenia with increased risk of fall and diabetic bone disease cause by the type 2 diabetes mellitus which is very frequent among obese subjects. Increased cortical porosity as well as alteration of bone matrix quality to the advanced glycation products is correlated to diabetic fracture risk while BMD remain inadequately normal. The correlation between obesity and fall also associates with prior diagnosis of chronic heart disease, severe depression/anxiety, chronic use of anti-depressants or sleeping pills, and sedentary lifestyle. A new map of fractures is drawn since obesity involves a higher risk of ankle (most frequent site in obesity) and humerus fractures and a lower risk of vertebral and hip fractures. The fracture healing is difficult in obese subjects due to inflammation and co-morbidities especially diabetes. Obesity has a rapidly rising prevalence so are the associated conditions; among them fragility fractures at specific sites represents an alarming new issue despite the traditional theories that obesity protects against osteoporosis.

Keywords: Obesity; Body mass index; Ankle; Fragility fractures; Osteoporosis

Introduction

Obesity represents a worldwide economical, social, and medical problem due to its large prevalence, to the decreasing age of onset and due to the correlated conditions (high blood pressure, type 2 diabetes mellitus, insulin resistance, liver steatosis, atherosclerosis, arthritis, respiratory insufficiency, acute and chronic heart ischemia, stroke, etc. [1-3]. These aspects seem to affect different countries with various levels of incomes, habits, and cultures [3]. Despite the large constellation of associated diseases the traditional aspects regarding the obesity-related bone status consist in fracture protective effect provided by the fat mass and by the increased levels of estrogens which are derived from the fat tissue [4]. Recent human and animal studies support the idea that obesity might not be protective for any type of osteoporotic fracture while the panel of skeleton anomalies involves also vitamin D deficiency, the type 2 diabetic bone disease, sarcopenia, etc. [5]. The overlap between population suffering from both osteoporosis and obesity causes a dramatic economical burden because of the epidemiological impact and associated costs. New directions are opened in order to find common therapies for pathogenic pathways involving both adipose tissue and bone formation as TGR5 signaling pathway, H^+ - ATP synthase, etc. [6].

General data

Body mass index: Body Mass Index (BMI) is directly correlated to Bone Mineral Density (BMD) as reflected by central Dual X-Ray Energy Absortiometry (DXA). So far BMD is the most powerful predictor of a fragility fracture for current clinical practice. Based only on this aspect it seems that obese females and men associate a lower risk of fracture. But in fact the protection is not against any type of fracture since the fracture risk includes not only quantitative parameters of the bone (as DXA reveals) but also qualitative aspects, and the risk of fall which are affected in obese subjects [7]. Busselton Healthy Ageing Study in Western Australia proved on 1929 Caucasian subjects a weaker positive correlation BMD-BMI at high BMI levels especially in men and lumbar BMD. Fat mass as well as lean mass were predictors of central BMD for the entire group (including after adjustment for confounding factors) aged between 45 and 66 years [8]. Nottingham Fracture Liaison Service included 4299 subjects with a low trauma fracture and 30% of them were obese (mean age of 67.1 ± 9 years). The prevalence of osteoporotic T-score among them was 13.4% compare to 40.4% in normal weighted persons, with an odds ratio for having osteoporosis of 0.23 (95% CI 0.19-0.28, $p<0.01$) compare to the same group [9]. The correlation coefficient r between BMI-BMD in obese versus non-obese persons were: 0.05 ($p=0.08$) vs. 0.25 ($p<0.001$) for lumbar DXA; 0.06 ($p=0.03$) vs. 0.21 ($p<0.001$) for femoral neck DXA, and 0.23 ($p<0.001$) vs. 0.32 ($p<0.001$) for total hip [9]. A recent cross-sectional study from Kosovo found that BMD is higher in obese menopausal females and men when compare to normal weighted and over weighted controls (according to central DXA results at hip and lumbar spine) but the results were not significant for lumbar BMD in pre-menopausal women [10]. Statistical data as Pearson's correlation revealed that weight (not only BMI) is

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positively correlated with BMD while, as expected, age is negatively associated [11]. Other clinical measurement reflecting obesity is hip circumference (HC). National Health and Nutrition Examination Survey enrolled 5287 patients between 2005 and 2006 and the results based on a multivariable analysis showed a positive statistically significant correlation of HC (as well as BMI) with lumbar and femoral neck BMD concluding that HC may be most useful to measure the relation to BMD [12]. Based on numerous traditional and modern data BMI is more useful to describe obesity and its grades and BMI correlation with BMD suggested the "advantage" of obese population in this matter but other studies revealed that some types of fractures are more prevalent at high BMI so other mechanisms are actually involved [13-15].

Bone turnover markers: The bone remodelling markers were found modified in obese population and animal models. It is difficult to establish what their exact active role on fracture prevalence is. Animals studies on male OLETF rats (sedentary, hyperphagic) found a higher percent of body mass fat than controls, as expected, with insulin resistance by week 13 and diabetes by week 40 [16]. By week 13 the bone formation marker P1NP as well as BMD were lower and by week 40 decreased bone formation markers as osteocalcin is registered suggesting that skeleton anomalies are detected early during progressive obesity affecting the bone strength to fractures [16]. High BMI associates increased body mass that elevates the mechanical loading of the skeleton and concurrently decreases the bone quality. Mice models confirmed the fact that obesity-related changes are presented during a two phases processes: initially a higher bone mass than control is registered causing the mechanical load and secondary the decreased levels of bone formation markers as assessed by calcein labelling are associated with increased marrow fat content [17]. A recent study in menopausal women found that osteoprotegerin as bone resorption marker ($p<0.05$) and bone alkaline phosphatase as bone formation marker ($p<0.01$) are statistically significant lower in osteoporotic obese subjects compare to obese with T-score > -2.5 or compare to control group without osteoporosis neither obesity ($p<0.001$, respective $p<0.01$) [18]. Controversies still exists in this field. For instance, a study on 197 subjects including 49% obese subjects found that blood alkaline phosphatase (ALP) was statistically significant higher in these (BMI of > 27 kg/m^2, 214 +/- 64UI/L versus 184 +/- 5 UI/L in non-obese) [19]. ALP had a 4.5%, respective 15% increase in over- weighted, respective obese subjects compare to normal weighted [19]. ALP is positively correlated with BMI ($r=0.3$, $p=0.0001$) [19]. In addition to obesity type 2 diabetes mellitus also influences the bone remodelling markers. A study on obese menopausal Saudi subjects showed that bone formation marker osteocalcin is significantly lower in diabetic women associating obesity when control to healthy population ($p<0.004$) while calciotropic hormones as parathormone showed no differences [20]. The bone markers status is probably correlated with adipogenesis pathways and fat-derived cytokines. A study on 265 obese subjects (one third of them had low BMD at central DXA) found significantly higher crosslaps as bone resorption marker and IL6 in osteopenic participants versus non-osteopenic participants while BMD was lower in the group with PPARγ high expression (peroxisome proliferator-activated receptor γ) suggesting that PPARγ represents a link between bone loss and fat excess [21]. Opposite to these results a study on menopausal women showed that adipose tissue hiper-production of leptin and adiponectiin may protect from bone loss by interfering with osteoprotegerin/RANKL ratio (by inducing an osteoprotegerin excess) [22]. Despite common mechanisms involving a correlation between a high BMI and the bone markers a cause-effect relationship is yet difficult to be established. A Chinese study on 2032 healthy adult females (pre and postmenopausal) suggested that osteocalcin may regulate the energy metabolism by negative correlation with BMI ($r= -0.13$, $p<0.001$), weight ($r= -0.08$, $p=0.002$), and fasting plasma glucose ($r= -0.13$, $p=0.001$) [23]. Whether osteocalcin is an innocent marker of bone loss in obese and/or diabetic patients or it plays an active role on bone- derivate insulin-resistance is still a matter of debate [24-26].

Fat-associated hormones and cytokines: Obesity associates a large panel of hormones and cytokines with opposite effects on bone. The fat tissue produces adipokines which are hormones with various roles into the human body as energy balance, satiety and food behaviour [27-29]. Adiponectin and leptin play a controversial role (up to this moment) related to the bone mass and density. Leptin is higher in osteoporotic obese females compare to osteoporotic non-obese women [27-29]. The primary menopausal osteoporosis is related to estrogen loss due to ovarian inactivity. On the contrary, in obese population there is an excess of estrogens provided by aromatase conversion. Obesity also associates androgens excess and insulin resistance with positive effects on bone mass [29,30]. But the risk of fractures in persons with high BMI is due to others non-gonadal hormones as growth hormone, insulin, angiotensin II and insulin-like growth factor-1, ghrelin that directly regulate the bone cells but also the pathogenesis of metabolic complications as high blood pressure or type 2 diabetes mellitus [30-32]. Higher values of BMI or levels of fat mass are associated with higher values of serum leptin and inflammatory markers as high sensitive C-reactive protein (hsCRP) and interleukin-6 (IL-6) when compare with subjects with low fat levels [33]. Murine experiments on LGXSM recombinant inbred strains proved that high fat diet slightly increased the trabecular density opposite to leptin increasing during weight gain while the genetic correlation with bone-fat changes was not statistically significant regarding 20 genomic locations [34]. This raised the question if the mechanical load is more likely a secondary event due to the fat load and not to a genetic predisposition [35]. Also fatty rats' models suggested that diet-induced obesity up regulates the osteoclastogenesis process (increased levels of RANK/RANKL is caused by fat-related TNFα via NFκB [36]. *In vivo* studies on menopausal obese women also did not found a correlation between the interleukin-6, IL-6 receptor, estrogen receptor alpha 1, low-density lipoprotein receptor-related protein 5, SP7 genes and BMD values on DXA so no clear genetic background is yet established in fracture risk assessment on persons with high BMI [37]. In current practice the fat-associated cytokines assay is not very useful since the results from large cohorts are inhomogeneous so they display more likely an experimental value [38-40].

Confounding factors

Obesity associates skeleton anomalies that are not caused by fat mass excess itself but by co-morbidities. We mention the vitamin D deficiency that is correlated to the level of adipose tissue and metabolic syndrome. Current data are insufficient to explain a particular cause-effect relationship between them. There is an increased incidence of type 2 diabetes mellitus in patients with obesity and others metabolic complications and new data revealed the increased fracture risk in diabetic population. More than one third of type 2 diabetic persons associates obesity depending on studied population but the skeleton involvement is also seen in over- and normal- weighted diabetic subjects [41,42]. A relatively recent term was introduced namely sarcopenic obesity which might contribute to fracture risk by influencing the risk of fall [43,44]. Other factors contributing to fractures in obese subjects are different co-morbidities and medications influencing the gait and sedentary life. [45]. For instance, New South Wales study on subjects

older than 65 years found than obesity have 25% higher risk of falling (95% CI 1.11-1.41, p<0.0003) compare to non-obese and the factors correlated to obesity and fall are: the prior diagnosis of heart disease/ angina (t= -3.536, p<0.0001); the previous diagnosis of depression/ anxiety (t=3.038, p=0.002), the use of specific medication against depression (t=3.102, p=0.002), the use of sleeping pills (t= -5.452, p <0.0001), sedentary habits defined by sitting for >8 hours/day (t=5.178, p<0.0001) [46].

Hypovitaminosis D: Most of the studies agree that vitamin D deficiency is associated with obesity, regardless sex and race [47]. The lack of adequate levels of 25-hydroxy vitamin D is a supplementary factor of risk regarding the fall [48]. Many studies found a correlation between vitamin D status and metabolic complications but the exact cause-effect relationship is yet to be established [49]. For instance, a study on 163 obese Thai individuals including 59.5% women found an inadequate level of 25-hydroxy vitamin D (25OHD) in 90% of them and 25OHD is negatively correlated with body fat percent (r= -0.23, p=0.003), and positively with skeletal muscle mass (r=0.18, p=0.003), including after age-adjustment [50].

Sweet bones: Among obese people there is an increase incidence of type 2 diabetes mellitus and metabolic syndrome. Many recent studies proved that in these conditions central DXA assessment has a limited utility since quantitative changes (as BMD) are similar to control groups who do not associate metabolic anomalies [51,52]. The diabetic bone associate a high risk fracture not related to BMD but to qualitative changes as increased cortical porosity, the bone matrix damage due to altered matrix by glycation process, etc. [52,53]. Also in diabetic patients there is an increased risk of fall in cases with a BMI higher than 35 kg/sqm, which seems to be independent from aging [54]. The disease brings other skeletal disorders impairing daily activities as amyotrophy, carpal tunnel syndrome, joint pains and chronic inflammation, neuropathy affecting the gait [55].

Sarcopenic obesity: A decline in muscle mass was described in obese men and women as seen in other chronic diseases with sarcopenia but there are difficulties in current assessment and definition of this condition [56]. A secondary term "dynapenia" refers to muscular function decline [57]. The fat gain involves fat infiltration and redistribution, pro-inflammatory environment, increased oxidative stress, impairing the daily physical performance, and reducing the movement which in addition to skeleton anomalies increases the fracture risk, a phenomenon called osteosarcopenic obesity [58]. The most exposed population to this aspect are women in menopause due to additive estrogen depletion. The others contributing factors to sarcopenia are reduced physical activity in obese subjects and potential endocrine co-morbidities as hypothyroidism, hypogonadism, chronic hypercortisolemia, low Growth Hormone (GH) - Insulin-like growth factor-1 (IGF1) status [59].

Fractures map: Since some fractures in obese have a similar prevalence as seen in general population and some are more frequent a new fracture map is described in relationship to the high BMI values. Overall there is site-specific relationship between fat mass and bone. The "white" aspect related to obesity related fractures is that actually the condition protects against adult hip and vertebral fractures while the "black" part is the fact that a higher risk of humerus and ankle fractures is seen [60]. Others studies found the distal forearm fractures more frequent in early menopause [61]. The technical explanation of the predilection consists not in BMD changes but in the risk of fall. Increased weight limits the normal movement and gait [62]. The kinetic data showed that the walk is similar to normal weighted people except for the fact they display a larger step width and a higher transversal friction is demanded (while the forces for the horizontal direction are similar) [63]. The most common fracture site in obese subjects is ankle [60,62]. A study on 280 ankle fracture revealed that a BMI ≥ 30 kg/ m2 (OR=1.78), men (OR=1.74) have higher chance of having Weber C type compare to type A and B while the diagnosis of low BMD according to DXA or the type 2 diabetes mellitus are not correlated to a more severe profile of the ankle fracture [64]. Nottingham Fracture Liaison Service found on 1285 obese men and women who suffered a previous osteoporotic fracture the following results when compare to non-obese people: the most frequent fractures were ankle (odds ratio of 1.48, p<0.01), upper arm (OR of 1.48, p<0.001) and the least frequent fracture was wrist (OR of 0.65, p<0.001) [9]. The results are applied in people younger than 70 years because in persons older than 70 risk of upper arm fracture was highest (RR=2.08, p=0.005) opposite to ankle and wrist which are not influenced by obesity [9].

Fracture history: Obesity increases the risk of complications after different types of fragility fractures. The large panel of metabolic complications as cardiac arrhythmia, ischemia, insufficiency, increases the anaesthesia risk if surgery is necessary. In cases when long period of immobilisation increases the thrombosis risk [65]. An analysis based on Pearl Diver Patient Records Database from USA found 20,319 subjects who underwent surgery for proximal humerus fractures by different procedures as open reduction and internal fixation (73%) and 18% of all had a BMI >30 kg/m^2 (ORIF group). This sub-group had a higher risk of 90-day local complications (OR=4.4%, 95% CI of 3.3-5.8, p<0.0001), and systemic complications (OR=4%, 95% CI of 3.5-4.6, p<0.0001) especially infections [66]. A particular aspect in fracture healing is related by the presence of uncontrolled diabetes on obese persons [67].

Paediatric obesity and fractures: An alarming young age of obesity is registered all over the world. Evidence showed that obesity-related fractures are site-dependent, mostly the upper limb or pelvis is involved [68,69]. Opposite to homogenous data related to low BMI and elevated fracture risk not all the studies in obese children found a significant higher risk of fractures [70]. Both the severity and the complications of the prevalent fractures may not be correlated increased BMI based on some observations but further studies are necessary [71].

Bariatric surgery: In order to reduce the obesity-related complications lifestyle changes are necessary. Lately one of the most used approaches in severe obesity is bariatric surgery. Despite obvious benefits many studies showed that a skeletal disturbance usually is not displayed immediately after the intervention [72]. A study on 2064 patients from Taiwan who underwent the procedure from 2001 to 2009 (included in National Health Insurance Research Database) were followed for 12 years and a 1.21-fold higher fracture risk (95% CI: 1.02-1.43) was seen comparing to obese subjects without surgery [73]. The risk seems to be related to malabsorption and it is elevated only 1-2 years after surgery [73]. A study on 258 residents from Minnesota who had bariatric surgery between 1985 and 2004 revealed after a 7.7 years of follow-up an increased fracture risk of 2.3-fold (95% CI: 1.8-2.8) for any fracture (the most affected sites were hip, spine, wrist, and humerus) [74]. Others mechanisms involve a 10% decrease of femoral neck BMD after 12 months but there is still a matter of debate if DXA define best the fracture risk assessment in this particular population [75]. Also the neurohormonal status is changed as well as bone turnover markers levels [76-78].

The skeleton anomalies related to obesity as well as increased fracture risk according to a site-specific pattern are necessary to be

known in order to prevent and treat them. The obesity needs a complex multidisciplinary approach and the control of the disease unfortunately does not always decrease the fracture risk as theoretically expected so a close follow-up is still necessary.

Conclusions

Obesity has a rapidly rising prevalence so are the associated conditions; among them fragility fractures at specific sites represents an alarming new issue despite the traditional theories that obesity protects against osteoporosis. Further studies are necessary to reveal the exact fracture phenotype in obese population. The prompt intervention in order to obtain the weight control as well as the metabolic improvement is necessary and lifestyle changes are useful. However bariatric surgery may associate an increased fracture risk after at least one year from the procedure.

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