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Obesity and the Effects of Excess Adiposity on Bone Properties, Health, and Function

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This article aims to inform on the relationships that exist between obesity, a fairly modern ailment to the human species, and bone mechanical properties and function. Because the phenomenon that is obesity is so contemporary, it's progressive effects on the skeletal system are poorly understood. Many previous studies aimed to prove that obesity had a positive effect on bone mass. It was believed that obesity and the excess body mass attributed to it essentially increased BMD by presenting load bearing bones with higher levels of stress than their non-obese counterparts, but this assumption of a positive correlation seems to be confounded by a variety of biological and endocrinological factors. The following sections will explore the effects that diets high in saturated fats and its consequence, obesity, have on the absorption of dietary calcium. This flaw in the absorption of dietary calcium may mean the decreasing ability of bone, particularly trabecular bone, to maintain proper density and in turn, become increasingly brittle. Combined with the increase in mechanical loading regimes that excess adiposity may present weight-bearing bones with, an understanding of these combined effects on bone biology is pivotal. This paper will also explore the relationships that exist between obesity, serum leptin levels and inflammatory responses, and bone properties. All of these factors (calcium absorption, leptin, and inflammatory responses) are important for bone growth, function, and mechanics, especially in respect to senescence. The previously mentioned "side effects" of obesity are also recognized as factors in the initiation of osteoporosis. Consequently, there must exist a relationship between obesity and osteoporosis. The bulk of this article will further explore this refined relationship in order to prove that the effects of obesity are indeed deleterious to health, and ultimately, to the function of bone as well.

Introduction

Obesity, the condition characterized by a body mass index (BMI) [3]30, is a unique epidemic to the modern human species. A novel environment, consisting of an abundance of high caloric foods such as simple carbohydrates, proteins, saturated fats, and sugars and a decrease in adequate levels of daily exercise, has presented novel consequences. The human species has evolved an efficient mechanism (involving fat cells in adipose tissues) for storing excess energy in the event of malnutrition and starvation, in which the release of free fatty acids to be used throughout the body would occur. Fortunately and unfortunately, this mechanism has presented a conflict of interest between economics and biology. It is fact that obesity is a direct risk factor for such conditions as non-insulin dependent diabetes mellitus (NIDDM), cardiovascular disease (CVD), hypertension, and certain cancers. It is highly likely that the effects of obesity are wider ranging, and the structural and storage functions inherent to the skeletal system make it a likely candidate for the effects of obesity to act upon.

Incidences of obesity have consistently been increasing in all parts of the globe and among all ethnicities in the past few decades. Data derived from the National Nutrition and Health Examination Surveys, provided by the Centers for Disease Control, have shown that the percentage of American adults defined as obese has increased from 14.5% between the years of 1976-1980 and 30.5% between the years of 1999-2000, to 37.5% between the years of 2001-2006 (CDC, 1982; CDC, 2008; Ogden et al., 2012). The condition has truly become an epidemic among affluent societies and the biological underpinnings of obesity are foundational for its understanding, and ultimately, its prevention and cure.

Biology of Obesity

Obesity is the product of ill-regulation of energy intake and energy expenditure, controlled by endocrine and neural pathways. It is important to realize that although the above statement sounds simple enough, obesity is not a problem of food intake control or energy expenditure. It is a more holistic process integrating the various finer mechanisms of appetite, energy balance, and energy expenditure. Energy balance is achieved through a complex interaction between hormonal and neural signals that subsequently affect the regulation of appetite and energy expenditure. This process of adaptive energy balance is primarily regulated by an adipocyte-derived hormone known as leptin, whose functionality can be influenced by dietary, hormonal, surgical, transgenic, and mutational means (Trayhurn, 2005). Appetite is largely under hypothalamic control, with a number of hormones, metabolites, gut peptides, and neural afferents affecting its positive expression (orexigenic) or negative suppression (anorexigenic) (Flier and Maratos-Flier, 2013). Leptin is also recognized as a primary peripheral signal, released from adipose tissues to interact with orexigenic and anorexigenic pathways in the hypothalamus (Trayhurn, 2005). Energy expenditure is a compilation of many factors, the most important being diet-induced thermogenesis. The significance of this function has provided succinct evidence in animal models but remains largely inconclusive in human models. This is likely because the organ responsible for the majority of thermogenesis, brown adipose tissue, is only present in minuscule amounts in the adult human (although it is very prominent in human infants). What is clear is that leptin, again, also plays a role in energy expenditure, in that the hormone provides an increased capacity for diet-induced thermogenesis (Flier and Maratos-Flier, 2013; Trayhurn, 2005). White adipose tissue (WAT) is also important in understanding the biology of obesity. Adipose tissue is not just an energy-storing organ; it is an active endocrine tissue. It is the primary site for the release of numerous molecules, by adipocytes, important in the regulatory functions mentioned above and other functions that will be mentioned throughout this paper. These molecules include leptin, cytokines such as IL-6, and proteins such as adiponectin (Flier and Maratos-Flier, 2013).

Bone and Mechanical Loading

Bone is a dynamic tissue that has the ability to reflect mechanical loading history throughout life. This phenomenon, formally known as the Bone Functional Adaptation model (or generically, Wolff's Law) involves the processes of basic bone molecular units (BMUs) and induced mechanical loading to change bone cross-sectional properties (which include such measures as BMD). Osteoblasts, bone forming cells, and osteoclasts, bone destroying cells, work in tandem in order to effectively adapt bone to its changing mechanical environment (Ruff et al., 2006; Pearson and Lieberman, 2004). This process is known as bone remodeling and differs from bone modeling in a couple of ways, including the fact that remodeling primarily occurs in mature bone due to increased mechanical loading and is a symmetrical process. Unlike modeling, remodeling works to evenly replace new bone at an identical rate and in identical amounts that old bone was destroyed. Alternatively, modeling is a process defined by changing the length and shape of growing bone.

Obesity, Bone, And Mechanical Properties

A key argument that arises when discussing the bone/obesity relationship is the notion that increased body mass, and the increase in mechanical loading that such mass presents on bone, is beneficial by increasing bone mineral density (BMD) and subsequently prevents such disorders as osteoporosis and bone loss (Robling and Turner , 2006; Felson et al., 1993; McClung et al., 1999). Some authors have gone so far as to hypothesize that obesity strengthens some biomechanical properties of bone (Brahmabhatt et al., 1998). It is true that body mass has a positive effect on bone health and that weight loss promotes bone loss, but whether or not mass derived from obesity or excessive fat accumulation is beneficial to bone has yet to be established. More recent studies tend to reject the previous ideology of obesity being beneficial for bone, and accept the idea that obesity has a negative effect on bone properties, especially cortical area (CA), trabecular bone volume, and bone mineral density/bone mineral content (Cao et al., 2009; Whiting, 2002; Pollock et al., 2007; Zhao et al., 2008).

In the past few years, the negative effects that obesity has on bone have become evident, especially in obese children (Pollock et al. ,2007; Whiting, 2002; Goulding et al., 2000; Weiler et al., 2000). This is likely the case because age specificity on the mechanical loading of bone exists. A declining response to mechanical loading by bone is seen after adolescence, and so the effects of obesity on bone will be most prominent during this life stage, whether positive or negative. Unfortunately, in children, increases in weight often precede an increase in BMD/BMC. Because the body has little time to compensate for the weight gain, bones are relatively more fragile based on body weight requirements and fracture occurs before positive bone accrual from the increase in loading due to weight does (Whiting, 2002). Whether obesity incurred by a high-fat diet has similar detrimental effects on the bones of mature animals when peak bone mass and strength have been achieved remains to be determined because these effects can often be obscured by the simultaneously occurring effects of senescence on bone in humans.

This divide in contemporary literature on the effect of such a prevailing health condition, obesity, on such a foundational organ, bone, leaves many questions to be answered. The inability to easily decide what effects bones incur from an obese state stems from multiple experimental and statistical sources, including differences in techniques used to analyze obese bone and measure fat content in subjects, age and maturation status of individuals, and inconsistencies in experimental sites and statistical modeling. It appears that additional methods for determining the effects of obesity on bone must rely on analyzing factors besides only bone cross-sectional properties and mechanics. Bone properties, health, and function can be influenced by obesity through a number of mechanisms common to both the condition and the organ.

Biological Connections Between Bone and Obesity

As cited by Rosen and Bouxsein, obesity and osteoporosis (a condition closely regulated by osteocytic and osteoblastic activity) share many features with each other. This represents an accurate depiction of the underlying biological relationship that exists between obesity and bone. The most revealing of these biological relationships is the fact that adipocytes and osteoblasts are derived from a common pluripotential mesenchymal stem cell (Cao et al., 2009; Cao, 2011; Rosen and Bouxsein, 2006). This being said, marrow adipogenesis may be inversely related to osteoblastogenesis; obesity may increase adipocyte differentiation and the accumulation of fat while simultaneously decreasing osteoblast differentiation and thus bone formation. This process appears to be endocrinological, specifically because regulation of this differentiation can be determined hormonally through feedback loops (Lee et al.). With this knowledge, further relationships can be delineated between the processes of obesity and its effects on bone.

Leptin

Leptin, the adipocyte-derived hormone described earlier, has been shown to be a major regulator of bone remodeling through osteoblastic activity. This is most likely due to the fact that leptin appears in tandem with the evolution of the bony skeleton (Karsenty, 2006). The hormone appears in higher circulation levels in obese individuals, but leptin receptors are disproportionately low. This produces an inability for the majority of circulating leptin to bind to its corresponding receptor and thus suppress appetite, induce energy expenditure, or regulate adaptive energy balance effectively. Leptin-deficient obese mouse models, referenced as *ob/ob* mice, which are genetically mutated to confer leptin deficiency, are often cited as evidence that leptin indeed has a direct effect on bone. This was first recognized by Ducy et al. and continues to be expanded upon. Initially, *ob/ob* obese mice were shown to have increased BMD, cortical thickness, and trabecular bone volume (Ducy et al., 2000). However, more recent research has revealed a positive correlation between leptin levels and BMD, cortical thickness, and trabecular bone volume (Cao et al., 2009; Hamrick et al., 2004). Diet induced obesity in mouse models has also presented identical evidence (Cao et al., 2010). Why has evidence of leptin's effect on bone properties changed in recent years? It is not entirely clear in the literature, but a possible reason may be the increase in understanding of leptin's complex actions on bone, specifically, its diverse ability to act directly on peripheral tissues or negatively through a central mechanism acting on the sympathetic nervous system. This may mean that the mechanism by which it acts depends on a multitude of factors, including but not limited to degree of sympathetic innervation at tissue sites, leptin resistance that may exist at the hypothalamic level (due to abnormally high levels of circulating leptin), and bone marrow hormonal composition (due to fat infiltration of marrow), and may affect bone accordingly (Hamrick et al., 2004; Thomas, 2004). In other words, leptin may have the ability to act positively *and* negatively on bone properties. What is clear is that leptin levels, which are directly related to the presence and amount of adipose tissues, have what is now accepted (and has proven) to be negative effects on bone properties.

Inflammatory Responses

Obesity has just recently been recognized to be associated with chronic low-grade inflammation. A number of inflammation related proteins in the cytokine family are secreted by adipocytes in white adipose tissues, the most important of these being tumor necrosis factor-a (TNF-a) and interluekin-6 (IL-6). It is believed that inflammatory factors, such as the ones above that originate in adipose tissues, may play a causal role in what is termed the "metabolic syndrome" of obesity. This metabolic syndrome refers to the many additional pathologies associated with an obese state (Trayhurn, 2005; Cao 2011). Evidence for this is cited by the fact that adipose tissue and circulating levels of such cytokines are proven to be elevated in obese subjects (Bastard et al., 2000; Bullo et al., 2003). Circulating levels of adiponectin, reported to have anti-inflammatory properties, are also shown to be decreased in obese subjects

(Trayhurn, 2005; Cao 2011). Leptin, the adipocyte derived protein described earlier, is also cited as stimulating inflammatory responses in obese individuals (Cao 2011).

In bone, equilibrium between bone resorption and bone formation is crucial for maintaining bone health and function. Any disruption in this equilibrium presents the ability for bone pathologies to manifest. It has been established that osteoblasts have the ability to regulate osteoclast activity and recruitment through the expression of the receptor activator NF-kB ligand (RANKL) and the osteoprotegerin (OPG). Pro-inflammatory cytokines, such as the ones described previously, are key mediators in the processes of bone resorption and osteoclast differentiation (Cao 2011). This fact as been proven in many studies that demonstrate the positive correlation between upregulation of RANKL and an increase osteoclastic activity, which leads to increased bone resorption in postmenopausal women. The fact that this menopause induced bone loss is also linked to the increased production of the pro-inflammatory cytokines that initiate the osteoclastic activity provides further evidence of this (Cao 2011; Eghbali-Fatourechi et al., 2003). It has also been proven that direct infiltration by fat into the marrow of bone has an identical effect. This marrow fat not only suppresses osteoblastogenesis, but might also promote bone resorption, because like fat cells elsewhere in the body, adipocytes within marrow secrete the same pro-inflammatory cytokines capable of recruiting osteoclasts. Bone marrow samples from women with osteoporosis have been shown to have a pronounced accumulation of adipocytes relative to the marrow of healthy, young subjects (Rosen and Bouxsein, 2006). High fat-diet induced obese animals have also exhibited increased bone marrow adiposity accompanied by reduced BMD in different skeletal sites (Cao 2011). Although there appears to be a positive association between fat infiltration in the bone marrow and skeletal fragility, the underlying mechanisms remain to be entirely fleshed out. However, it is clear that bone marrow adipogenesis increases with conditions that induce bone loss, such as estrogen depletion, disuse, and hindlimb unloading (Pollock et al., 2007). This mechanism, coupled with the negative effects of leptin on bone BMD, trabecular bone volume, and cortical thickness presents the bones of obese individuals with a variety of disadvantages. Because leptin has also been recognized as an initiator of inflammatory responses, a state of obesity will result in a cascade of negative effects on bone properties by means of the above mentioned pathways.

Calcium Absorption

Diets high in saturated fat can produce deleterious effects on the absorption of dietary calcium, and consequently, adverse effects on bone mineralization particularly in growing animals. This reduced intestinal calcium absorption is attributed to a condition termed hypercalciuria, which manifests from hyperinsulemia. This condition is characterized by the accumulation of calcium soaps created by an abundance of free fatty acids, stored fats released by white adipose tissues. These calcium soaps have an inability to be absorbed and are insoluble (Cao 2011). This creates a deficiency in circulating and potentially available calcium throughout the body. Interestingly, many animal studies have shown significant reduction in trabecular bone properties (geometric structure and mineral content) but not in cortical bone properties. Cao et al., in their experiments on high fat-diets in adolescent mouse models, have shown decreases in trabecular bone mass but no changes in cortical bone mass . Similarly, Wohl et al. found that high-fat diets in roosters yielded significantly lower mineral contents and bone mechanical properties in the trabecular bone of adult roosters. The significance of the similar results obtained from these studies elucidates the effects that diets high in fat content have on not only growing bone, but mature bone as well. It was stated previously that juvenile and adolescent bone is more receptive to modeling and remodeling, which primarily occurs in cortical bone, but trabecular bone changes appear to be responsive in growing, as well as mature bone. This has been attributed to trabecular bone's greater surface area to volume ratio compared to that of cortical bone (Cao et al., 2009). This shows that in the adult model, trabecular bone is more vulnerable to mineral fluctuations than cortical bone, thus an inadequacy in intestinal calcium

absorption in animals may be more apparent in mature trabecular bone. This can be explained by that fact that high fat diets, as has been explained, do not inhibit mineralization, but rather, increase bone resorption. However, it has been shown that overweight and obese individuals tend to have lower concentrations of circulating vitamin D (Pollock et al., 2007). Vitamin D is a key regulator of calcium and phosphorus levels in the body, and its deficiency will consequently lead to a deficiency in these other minerals, namely calcium. Calcium deficiency may in turn lead to poor mineralization of remodeling bone, and so, the effects of poor absorption of calcium in the intestine may prove to be a mechanism by which high fat diets and obesity can inhibit mineralization as well as promote increased bone resorption.

Conclusions

It is a well-documented fact that BMD is positively correlated with body mass, but what must be realized is that increased body mass does not necessarily mean an increase in fat mass. Obesity, which is notorious for its wide-ranging effects on other physiological functions, has an unsurprising effect on the skeletal system as well. Although the "positive" effects of increased mechanical loading on the bones of obese individuals may be apparent, these effects are not enough to overcome the detrimental effects that obesity incurs on bone molecularly, chemically, and biologically. Adults suffering from obesity may incur the greatest risk of bone fragility, due to the effects of senescence and its associated pathologies which obviously increase with age. Children, on the other hand, may incur the least risk of bone fragility, given that they engage in adequate amounts of exercise while young. This is because exercise in children is what accounts for the majority of bone mass accrual during this life stage. Even so, the progressive effects of obesity in children, given that the condition will have manifested sooner and will have significantly longer amounts of time to affect bone throughout life, will likely manifest with identical levels of bone degeneration as is seen in the onset of obesity during adulthood.

Leptin, a key hormone derived from adipocytes, plays a major role in obesity as well as bone health, and this relationship has been evident for at least the last decade. This is likely because of the fact that leptin has a close evolutionary relationship with the skeleton. Recently, it appears that the increased levels of circulating leptin in obese individuals contributes to a decrease in bone mechanical properties, including decreased BMD, cortical thickness, and trabecular bone volume. The newly discovered, multiple mechanisms with which leptin interacts with bodily systems is complicated and continues to be studied.

Inflammatory responses seen in obesity also affect bone in a multitude of ways. Cytokines such as IL-6 and TNF-a regulate osteoclastic activity through RANKL/OPG pathways; thus, increasing levels of pro-inflammatory cytokines results in increasing osteoclastic activity. Leptin, known for its inflammation inducing properties and high circulating levels in obese individuals, works to enable the continuation of this process. Increased osteoclastic activity, again, results in the degradation of bone properties by the upregulation of bone resorption and downregulation of bone formation.

Poor absorption of dietary calcium is another result of obesity that influences bone health, function, and properties. Calcium soaps, deposited by free fatty acids, are insoluble and cannot be absorbed. Trabecular bone seems to be more sensitive to the effects of mineral deficiencies than cortical bone. This may explain why the findings of many studies support changes in trabecular bone properties but not cortical bone properties in obese subjects. Up until this point, all evidence supports the fact that the effects of obesity do not inhibit mineralization of bone, but rather, increase bone resorption. Evidence of consistently low vitamin D levels in obese individuals may alter the truth of this statement.

Many flaws are inherent to the study of the obesity/bone relationship and to this argument. The largest of these flaws is that much evidence derived for (and even against) this argument

involves animal modeling. These animals, usually mice, are subjected to an obese condition for short periods of time that are only minimally applicable to the extended states of human obesity. Inducing diets in mouse models is also fundamentally different than the more complex diet-induced obesity in humans because the excessive consumption of proteins and minerals that are staples in a human diet, and which also affect bone metabolism, are foreign to the diets of mice (Cao 2011). Consistent modeling of the effects of high-fat diet induced obesity through longitudinal studies is needed. Also, more research using young to middle aged obese adults would help to tease out complicated trends attributable to age specific phenomena that occur distinctly in childhood and in old age. As any scientist will admit, minimally related animal models that yield positive or negative information are better than not attaining any information at all, and so the usefulness of these models and their application to human obesity must still be appreciated.

Research exploring the relationships between obesity and bone properties, health, and functions is novel, considering the contemporaneous appearance of the condition that is obesity. This research leaves many questions to be answered in the future. A classical question that studies of bone pose is that of the extent to which bone properties rely on pre-existing genetic material as opposed to mechanical loading in life. Could a genetic predisposition to obesity, sustained through multiple generations, confer an advantage for obese bone? Is bone inherently weak from birth in its ability to sustain conditions of obesity throughout life? The answer is not a simple, nor a clear cut one. What is obvious is that both genetics and mechanical loading play significant roles, respectively, in the growth and adaptation of bone. Also, if obesity and a biological state of increased adiposity are detrimental to bone, how much fat, if any, can be proven to be a protective mechanism for bone? A comparison between weight-similar, but BMI-differing, subjects could easily be made to determine the answers that this question poses.

Lines of evidence delineated above all succinctly point to the degenerative effects that obesity has on bone properties, health, and function. These degenerative properties seem to mimic those such as osteoporosis and osteoarthritis. This presents the possibility that these conditions may be included, with a long list of others, in what has already been coined the "metabolic syndrome" that accompanies obesity. The realization that obesity may be a risk factor for osteoporosis could be pivotal in the possibility of treating and even curing both conditions. As medical anthropology tells us, disease is never random in its occurrence, but rather, it is patterned. As scientists, our goal is to identify these patterns and define them. Obesity presents bone with such degenerative effects as decreased trabecular bone volume, increased osteoclastic activity, and decreased calcium availability. Obesity is likely a key risk factor for attaining osteoporotic bone, and scientific focus on this topic will likely expand as mass populations of individuals continue to suffer from a physiologic state of obesity.

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