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The evolving role of obesity in knee osteoarthritis

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Abstract

Purpose of review—The frequency of knee osteoarthritis continues to accelerate, likely because of the increasing proliferation of obesity, particularly in men and women 40–60 years of age at the leading edge of the ‘baby boom’ demographic expansion. The increasing pervasiveness of obesity and the growing appreciation of obesity’s accompanying metabolic/inflammatory activities suggest rethinking the knee osteoarthritis paradigm.

Recent findings—Whereas once knee osteoarthritis was considered a ‘wear-and-tear’ condition, it is now recognized that knee osteoarthritis exists in the highly metabolic and inflammatory environments of adiposity. Cytokines associated with adipose tissue, including leptin, adiponectin, and resistin, may influence osteoarthritis through direct joint degradation or control of local inflammatory processes. Further, pound-for-pound, not all obesity is equivalent for the development of knee osteoarthritis; development appears to be strongly related to the co-existence of disordered glucose and lipid metabolism. Additionally, obesity loads may be detected by mechanoreceptors on chondrocyte surfaces triggering intracellular signaling cascades of cytokines, growth factors, and metalloproteinases.

Summary—This review summarizes recent literature about obesity, knee osteoarthritis and joint pain. Consideration of adipocytokines, metabolic factors, and mechanical loading-metabolic factor interactions will help to broaden the thinking about targets for both prevention and intervention for knee osteoarthritis.

Keywords

adipocytokines; cardiometabolic clustering; knee osteoarthritis; obesity

Introduction

This review will address recent literature about knee osteoarthritis and obesity: two conditions whose prevalence is accelerating worldwide. The review includes the potential association of knee osteoarthritis and selected adipocytokines including leptin, adiponectin, and resistin, the group of cytokines related to fat cells. In addition, the co-occurrence of obesity plus cardiometabolic factors appears to alter risk of knee osteoarthritis as compared with obesity without these cardiometabolic factors. Considering interactions between mechanical loading and these metabolic factors can help broaden approaches to both prevention and intervention for knee osteoarthritis.

Osteoarthritis is a highly prevalent joint disorder estimated to affect more than 37% of adults over the age of 60 [1]; it is a leading cause of pain and disability. Osteoarthritis is associated

with considerable loss in productivity and healthcare expenditures, accounting for 97% of the total knee replacements and 83% of the total hip replacements in 2004 [2]. Using national data, the Healthcare Cost and Utilization Project showed that osteoarthritis accounted for US\$ 10.5 billion in hospital charges in 2006, making it a more expensive condition than pneumonia, stroke, or complications from diabetes. Hospital admissions for arthritis more than doubled from 1993 to 2006 [2].

The frequency of knee osteoarthritis continues to accelerate, likely because of the aging of the population and the increasing proliferation of the primary risk factor, obesity. There is an increasingly greater proportion of the total population, both in the United States and worldwide [3], over age 60, the age range typically associated with having osteoarthritis. Although the prevalence of obesity is rising in this elderly segment of the population, it is the escalating prevalence of obesity in those men and women aged 40–60 years, who are simultaneously at the leading edge of the baby boomer demographic expansion, that are the major contributors to the burgeoning osteoarthritis population.

Obesity has long been recognized as a risk factor for prevalent osteoarthritis, especially knee osteoarthritis [4–9] although the obesity definition based on a BMI more than 30 kg/m² was not widely adopted until the 1990s [10]. Data from a study of a general British population suggested that women in the highest tertile of BMI had six-fold increased odds of knee osteoarthritis (OAK) and nearly 18 times higher odds of bilateral OAK, compared with women in the lowest tertile of BMI [11]. Similarly, a study of US African-American and Caucasian women identified higher risk of prevalent knee osteoarthritis with higher BMI levels [12]. Longitudinal studies show that increased weight precedes the presentation of OAK; in a longitudinal study of men and women aged 40–64 years, Manninen *et al.* [8] reported that for every standard deviation increase in BMI (3.8 kg/m²), there was a 40% increased risk [relative risk (RR) = 1.4; 95% confidence interval (CI) 1.2–1.5] for developing OAK.

How does obesity increase the likelihood of having knee osteoarthritis?

Because of the magnitude of obesity as a risk factor for osteoarthritis, especially knee osteoarthritis, as well as the growing prevalence of obesity, including morbid obesity (BMI >40 kg/m²), there is new effort being developed to understand how obesity increases the likelihood of having knee osteoarthritis. These efforts have as their long-term goal the development of focused prevention and intervention efforts. However, not all obese persons develop knee osteoarthritis, nor are all individuals with OAK obese. Further, because BMI includes both fat and lean mass, the relative contribution of adipose tissue and muscle mass, and their contribution to muscle strength, cannot be disaggregated when using BMI as a measure of obesity. The understanding that, pound-for-pound, not all obesity is equivalent for the development of knee osteoarthritis has opened new avenues for study.

This review summarizes the obesity and knee osteoarthritis literature, including the few studies that have focused on joint pain. Potential mechanisms for observed obesity/pain and obesity/osteoarthritis associations are discussed, with special consideration to those shown to be most promising, including adipocytokines, metabolic factors, and mechanical loading.

Osteoarthritis, obesity, and adipocytokines

Rheumatoid arthritis has long been recognized as having a vigorous inflammatory component, and as a result, some treatments were directed at modulating the deleterious elements of that inflammatory response. In contrast, osteoarthritis was considered a ‘wear-and-tear’ condition with a minimal inflammatory response. However, this framework for considering osteoarthritis, especially knee osteoarthritis, is now shifting with the increasing

pervasiveness of obesity and the recognition of the inflammatory environment associated with obesity. Adipose tissue, once considered a passive storage portal of energy, is now recognized as a highly metabolic endocrine organ with the capacity to secrete active agents including adipocytokines, such as leptin, resistin, and adiponectin. Over the past decade, interest in these adipocytokines has quickly become an area of intense study with respect to osteoarthritis based on evidence that they may play an important role in cartilage homeostasis and because of their emerging potential as therapeutic targets.

Leptin, adiponectin and resistin levels have been detected in the synovial fluid and plasma of patients with osteoarthritis [13,14]. Important new findings of different patterns of distribution of these adipocytokines between the joint and circulating compartment suggest that the joint is a unique area of activity for adipocytokines and their presence may be related to local joint degradation effects. Resistin and adiponectin levels were greater in serum than in synovial fluid whereas leptin concentrations were highest in synovial fluid [15]. Leptin, adiponectin, and resistin are thought to influence osteoarthritis through direct joint degradation or through control of local inflammatory processes.

Leptin is generally higher in obese individuals; the extremely high amounts of circulating leptin have led investigators to suggest a leptin resistance syndrome as a parallel concept to insulin resistance. BMI and body weight are consistently associated with leptin levels among those with osteoarthritis. Leptin and its receptor have been identified in human chondrocytes, osteophytes [13,16], synovium, and infrapatellar fat pad [15], and may affect growth factor synthesis and anabolism. Examination of cartilage, subchondral bone, and osteophytes shows evidence of upregulated leptin expression. Leptin expression has been directly associated with the degree of cartilage degeneration [13,17], and synergistic relationships of leptin and proinflammatory cytokines have been reported [13]. Following administration of leptin, chondrocytes from osteoarthritic patients had increased production of IL-1b, MMP-9, and MMP-13. This suggests that mechanistically, leptin has a direct pro-inflammatory and catabolic role in cartilage metabolism [17] and leptin or its receptor may serve as a therapeutic target.

Although there has been extensive study of adiponectin and diabetes, less is known about the functional role of adiponectin and joint damage. Greater concentrations of adiponectin within the joint suggest an important role for adiponectin in osteoarthritis development. Adiponectin expression was 100-fold greater in the synovial fluid of osteoarthritis patients as compared with their plasma [14]. Furthermore, the adiponectin receptor AdipoR1 was expressed in cartilage, bone, and synovial tissues. Demonstration of downregulation of MMP-13 and upregulation of an associated inhibitor suggests that adiponectin may be protective in the progression of osteoarthritis [14].

Inflammation is an important hallmark of osteoarthritis, and the adipocytokines may be important in the modulation of inflammatory processes. Leptin and resistin levels may be associated with the promotion of inflammation but adiponectin appears to reduce production of pro-inflammatory cytokines [18]. Leptin enhanced expression of iNOS and COX-2 and production of nitric oxide, PGE2, IL-6, and IL-8 [19**]. Although Lago *et al.* [20] reported that adiponectin was able to increase IL-6, MMP-3, MMP-9, and MCP-1 levels, there was no modulation of the release of proinflammatory cytokines including TNF-a, PGE2, and IL-1b.

Osteoarthritis, obesity, and metabolic factors

In addition to the adipocytokines, obesity may generate other systemic effects related to osteoarthritis, including roles for disordered glucose and lipid metabolism. Metabolic changes resultant from insulin resistance and increased glucose load are closely related to

proinflammatory cytokine production, characteristic of a chronic inflammatory state. Furthermore, the formation of advanced glycation end products (AGEs) may be associated with increased collagen stiffness, alterations in the mechanical properties of the extracellular matrix, and decreased proteoglycan synthesis, thereby possibly resulting in cartilage degradation [21]. Notably, chondrocytes express the functional receptor for AGEs which, when stimulated with ligands, induces production of pro-inflammatory cytokines [22].

Early reports identified significant associations between knee osteoarthritis and hand/wrist osteoarthritis and cardiovascular risk factors (uric acid, cholesterol levels, hypertension, fasting plasma glucose) [23–25]. However, support and interest in the metabolic link with osteoarthritis diminished in the absence of consistent studies demonstrating associations between osteoarthritis and metabolic factors (glucose, lipids, and blood pressure). Namely, an influential report using data from NHANES-I did not support a metabolic link between obesity and knee osteoarthritis, although technical limitations were subsequently identified in study measures [6].

A recent report [26*] considered both obesity status and cardiometabolic risk factor clustering (including HDL-c, LDL-c, triglycerides, blood pressure, waist : hip ratio, glucose, and hsC-RP). Mid-aged women who were obese (defined as BMI ≥ 30 kg/m²) and had two or more cardiovascular risk factors had more than six times increased odds of having prevalent knee osteoarthritis as compared with nonobese women without cardiometabolic clustering. Interest in this paradigm has re-emerged with the identification of adipocytokines and their ability to explain underlying disorder and with the observation of important subgroups of individuals that appear to be at greater risk of osteoarthritis. Why some obesity is associated with intense metabolic activity whereas other obesity is less expressive of this metabolic activity remains to be determined.

Despite the attention that has been given to the role of metabolic factors as a potential mechanism for joint degeneration, few studies have examined differences in osteoarthritis prevalence or incidence with respect to disordered metabolic factors. Only recently have studies been implemented that incorporate information about adipocytokine levels that differentiate high-risk susceptible populations for prevention and intervention.

Osteoarthritis, obesity, and mechanical loading

Obesity has the potential for a major impact metabolically in the presentation of osteoarthritis while concurrently contributing to a major mechanical load on the joint. Clinical and animal studies of joint loading have provided evidence that abnormal loads can lead to changes in the composition, structure, and mechanical properties of articular cartilage [27–29]. These abnormal loads have been attributed to obesity, joint instability, or trauma. Biomechanically, muscle forces are a major determinant of how loads are distributed across a joint surface. Decreasing the muscle forces acting about a joint or misaligned joints will ultimately alter loading conditions. Failure by the quadriceps to adequately absorb forces about the knee can cause greater dynamic loads being placed on the articular cartilage, resulting in progressive degeneration. As a result, quadriceps weakness has been shown to be an important risk factor for osteoarthritis in some [30*] but not all studies [31].

Muscle strength, assessed as torque, reflects the capacity to do work and is strongly influenced by body mass, but is differentially expressed with respect to skeletal muscle mass versus total body mass. Loss of muscle strength may reduce the shock-absorbing potential of the joint, thereby causing cartilage fibrillation [32]. Changes to the cartilage structure may initiate a local immune response, resulting in systemic inflammatory responses throughout the joint. Increased loading on the knee joint may be detected by mechanoreceptors on the

surface of chondrocytes; this may trigger intracellular signaling cascades of cytokines, growth factors, and metalloproteinases [33**].

The role of body composition, however, is not unique to the compartment representing skeletal muscle mass. Instead, it is likely that the relative contribution of the fat and muscle compartments may be important for muscle activation and function through the action of insulin. In fact, insulin resistance is often associated with the loss of muscle mass and the co-occurrence of fat mass gain. Nearly 10 years ago, Roubenoff [34] hypothesized that loss of muscle is the primary event for osteoarthritis onset, but this then contributes to fat gain, which then reinforces further muscle loss. Extending the concept of obesity to the role of body composition beyond traditional views of fat/lean compartments is important, as the process of fat gain and muscle loss may act synergistically within and around the joint to not only initiate joint damage, but also allow further progression through the effects of insulin and inflammatory processes.

Osteoarthritis, obesity, and pain

Because the definition or diagnosis of osteoarthritis, including knee osteoarthritis, is frequently conditioned upon the presence of pain, one must also consider the role of obesity in pain. There are a number of cross-sectional studies demonstrating increasing frequency of severe pain with increasing BMI. In NHANES III, increasing BMI was associated with higher prevalence estimates for knee pain (12.1% in underweight vs. 55.7% in obesity class III) and hip pain (10.4% in underweight vs. 23.3% in obesity class III) before and after adjusting for sex, race, and age [35]. There are few longitudinal studies to address the directionality of pain and obesity. In a British population-based study [36] of individuals over the age of 50 without knee pain, those who were obese were nearly three times more likely than those of normal weight to develop severe knee pain in a subsequent 3-year period. In a Dutch study, relative risks for developing pain over 6 years were 2.34 (95% CI 1.17–4.72) in obese men and 2.78 (95% CI 1.36–5.70) in obese women and adjustment for weight change did not change these associations [37]. Similar results were found for the associations between waist circumference and pain [37]. In exploring a reverse causal relation, analyses showed no significant associations between prevalent pain and weight gain [37].

There is limited understanding of how being overweight and/or obese is related to the pain associated with osteoarthritis, especially knee osteoarthritis. As reviewed by Janke *et al.* [38], there have been numerous mechanical-structural factors that have been proposed as mechanisms to explain the pain/obesity relationship. These include increased loading [39], joint misalignment [40,41], or changes in bone and joint structures. Studies of the development of patellofemoral pain syndrome (PFPS) in young, active, and nonobese adults have led to the development of biomechanical models of pain [42*] and consideration that there may be different causal relationships based on which joint compartment is affected.

Altered glucose homeostasis may represent the metabolic mechanism operating with regard to pain and obesity. In studies of acute pain in trauma and surgery, there is decreased insulin sensitivity and a reduced ability of insulin to suppress endogenous glucose [43]. In these same studies of induced acute pain, there were increases in circulating concentrations of epinephrine, cortisol, growth hormone, and free fatty acids [43], all substances associated with altered glucose homeostasis. Because obesity is frequently, though not always, associated with insulin resistance, altered glucose homeostasis may be an important state related to chronic pain.

Although the literature alludes to the potential role of inflammatory cytokines such as IL-6 and TNF-alpha as a component of pain, there is a dearth of literature to support this

relationship; likewise, there is little to support a role of the adipocytokines in relation to pain.

Conclusion

Despite much evidence to support an obesity–osteoarthritis–pain association, this is an area in need of additional work to further elucidate the complex ways in which excess adipose tissue may impact pain and joint damage. Unfortunately, the use of BMI alone as a measure of body composition does not adequately provide a means of understanding the physiological activities that could be relevant in relating obesity to osteoarthritis. BMI reflects both fat and lean mass and fails to characterize the amount of muscle mass and its contribution to muscle strength. Furthermore, BMI provides no information about the metabolic environment within an individual or the levels of adipocytokines that may contribute to osteoarthritis progression. Future work in the field should incorporate a variety of measures, including assessment of fat and skeletal muscle mass, adipocytokine levels, and cardiometabolic health status to appropriately characterize the multidimensional effects of obesity. In doing so, we may be better equipped to design interventions and treatment paradigms to better address the various effects of adipose tissue and most effectively target osteoarthritis.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 612–613).

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