Kelly S. Santangelo[a], Lauren B. Radakovich[a], Josie Fouts and Michelle T. Foster*

Pathophysiology of obesity on knee joint homeostasis: contributions of the infrapatellar fat pad

DOI 10.1515/hmbci-2015-0067
Received November 17, 2015; accepted December 15, 2015; previously published online January 22, 2016

Abstract: Osteoarthritis (OA) is a debilitating condition characterized by inflammation, breakdown, and consequent loss of cartilage of the joints. Epidemiological studies indicate obesity is an important risk factor involved in OA initiation and progression. Traditional views propose OA to be a biomechanical consequence of excess weight on weight-bearing joints; however, emerging data demonstrates that systemic and local factors released from white adipose depots play a role. Hence, current views characterize OA as a condition exacerbated by a metabolic link related to adipose tissue, and not solely related to redistributed/altered weight load. Factors demonstrated to influence cartilage and bone homeostasis include adipocyte-derived hormones ("adipokines") and adipose depot released cytokines. Epidemiological studies demonstrate a positive relation between systemic circulating cytokines, leptin, and resistin with OA types, while the association with adiponectin is controversial. Local factors in joints have also been shown to play a role in OA. In particular, this includes the knee, a weight-bearing joint that encloses a relatively large adipose depot, the infrapatellar fat pad (IFP), which serves as a source of local inflammatory factors. This review summarizes the relation of obesity and OA as it specifically relates to the IFP and other integral supporting structures. Overall, studies support the concept that metabolic effects associated with systemic obesity also extend to the IFP, which promotes inflammation, pain, and cartilage destruction within the local knee joint environment, thus contributing to development and progression of OA.

Keywords: adipokines; bone; degenerative bone disease; infrapatellar fat pad; joint; obesity; osteoarthritis.

[a]First author credit
***Corresponding author: Dr. Michelle T. Foster,** PhD., Department of Food Science and Human Nutrition, College of Health and Human Sciences, Colorado State University, 1571 Campus Delivery, 500 West Lake Street, Fort Collins, CO 80523, USA,
Phone: +(970) 491-6189, Fax: +(970) 491-3875,
E-mail: Michelle.Foster@colostate.edu
Kelly S. Santangelo and Lauren B. Radakovich: Department of Microbiology, Immunology and Pathology, College of Veterinary Medicine and Biomedical Science, Colorado State University, Fort Collins, CO 80523, USA
Josie Fouts: Department of Food Science and Human Nutrition, College of Health and Human Sciences, Colorado State University, Fort Collins, CO 80523, USA

Introduction

The prevalence of overweight and obese individuals is increasing worldwide. As of 2014, the US National Center for Health Statistics reported that ~70% of Americans are overweight with almost half further defined as obese [1]. Other regions of the world reported to have an increase of excessive weight and obesity in adults, as of 2008, include Southern and Central Latin America (~63% overweight, ~25% obese), Western and Eastern Europe (~48% overweight, ~23% obese), South African (~48% overweight, ~28% obese) and North Africa and Middle East (~60% overweight, ~28% obese) [2]. The rise in obesity is also associated with an increase in various health problems. Numerous epidemiological studies have associated excessive adipose tissue accumulation, as measured by anthropometric indices such as high body mass index (BMI), large waist circumference (WC) or high waist/hip circumference ratio (WHR), with many chronic diseases. It is best established that high BMI [3] and WC [4] are associated with a deleterious lipid profile including high triglycerides and non-HDL cholesterol and lower HDL. High lipid profiles and increased cholesterol subsequently increase risk for atherosclerosis and coronary heart disease; hence, these diseases are also associated with increased BMI [5, 6]. The link between obesity and dysregulated glucose homeostasis is also well established, with all estimates of obesity (BMI, WC and WHR) demonstrated to be positive association markers for non-insulin-dependent diabetes mellitus (type-2-diabetes) [7]. Several other obesity disease risk associations, as described with anthropometric indices, include certain cancers [8–11], infection susceptibility [12, 13], asthma

[14, 15], stroke [16, 17], and many more, including degenerative joint disease [18–20].

Degenerative joint disease is also commonly known as osteoarthritis (OA). Typical symptoms of this condition are joint pain, swelling, and stiffness. Therefore, OA is a type of joint disease associated with inflammation, which results in breakdown of joint cartilage and associated bone. Joints generally affected in OA include those in the finger, neck, back, hips, and knees. Because of this, OA can become debilitating and affect daily activities, leading to increased work disability [21]. OA is viewed as a chronic injury where prevention and early care are the primary modes of treatment. Therefore, modifiable risk factors such as joint injury, impaired muscle function, and excessive weight are primary targets for prevention. As previously discussed, those who are overweight/obese are at greater risk for the development of OA. It was traditionally proposed that this association is due to mechanical stress of excessive weight on joints; however, OA also occurs in non-weight bearing joints [22]. In addition, symptom relief from this condition is not associated with general weight loss, but rather weight loss that is specific to fat reduction [22]. This suggests OA is a condition primarily exacerbated by metabolic links that relate to fat and is less dependent on mechanisms related to loading.

Obesity and OA risk

Several epidemiological studies demonstrate that excessive weight and obesity are preventable risk factors of OA. Numerous different joints are affected by obesity; however, OA of the hip and knee have the highest correlation with increases in adiposity [23]. Although BMI has a noteworthy positive association with hip OA risk [24–26], the association between increased fat mass and OA development is stronger for the knee [27–29]. Therefore, this review will primarily focus on the pathophysiology of obesity on knee joint/cartilage homeostasis.

Obese/overweight individuals are roughly three times more likely to develop knee OA than those that are lean [30]. Indeed, as BMI increases by five units, risk of symptomatic knee OA accumulatively increases by ~10% [31]. In adults, moderate exercise and weight loss significantly reduce OA associated pain while improving physical performance [32]. It is proposed that, at the population level, ~30% of knee OA is avoidable with the reduction of BMI [33]; thus, obesity is a modifiable OA risk factor with high impact at the population level. Consistent with this, modest reductions in BMI are demonstrated to produce great reductions in disease risks, with a two-unit drop in BMI lowering knee OA risk by 50% [34]. Traditionally, decreased BMI-induced OA improvements were proposed to be related to reduced weight on load-bearing joints; however, obesity is also positively associated with hand OA [35, 36]. Because hands are not weight-bearing joints, this suggests the fundamental link between obesity and OA may be due to systemic factors. Much like BMI, type-2-diabetes is also associated with progression of knee OA. As measured via joint space narrowing, type-2-diabetes is associated with disease progression of OA [37]. Consistent with this, high hemoglobin A1c is associated with a greater risk for OA disease progression [38]. In addition, insulin resistance is also associated with OA prevalence [39].

Relation of systemic factors and OA

Obesity is causally linked to a cluster of chronic and complex diseases [40–45]. Adipose tissue dysregulation is a fundamental driver of the comorbidities associated with obesity. Specifically, inflammation induced by excessive adipose tissue accumulation appears to link obesity to disease risk [46–48]. Although short-term inflammation is a principal defense in response to injury, prolonged inflammation, as occurs in obesity, does not appear to be beneficial [49]. Hence, obesity is characterized as a state of chronic inflammation. The inability to alleviate inflammation leads to chronic diseases; thus, systemic inflammation caused by obesity may play a role in OA progression. Again, this is supported by epidemiological studies demonstrating increased risk of hand OA in obesity [35, 36].

A marker of low-grade inflammation commonly associated with obesity, C-reactive protein (CRP), is associated with decreased cartilage volume and disease progression of OA [50–52]. The primary regulators of CRP, IL-6 and IL-1, are also positively associated with knee joint space narrowing [53]. Radiographic OA (ROA) is similarly associated with increases in circulating IL-6 and CRP [54], as is TNF-α with radiological progression of knee OA [55].

Increases in adiposity are also associated with increases in adipose tissue derived hormones, also known as adipokines. Hence, systemic mediators that are increased with obesity are not just limited to increases in circulating cytokines, but also increases in adipokines. Adipokines increased with adiposity include, but are not limited to, leptin, resistin, visfatin, and chemerin. In opposition, adiponectin is one of the limited adipokines that is decreased in obesity. Epidemiological studies demonstrate an association between these adipokines and OA.

Leptin, produced from white adipocytes, is a lipostatic signal that regulates food intake and energy expenditure. It is recognized to play an integral role in inflammation, angiogenesis, and bone and cartilage metabolism [56–58]. Epidemiological studies support that increases in systemic leptin are positively associated with hip [58] and knee OA [59, 60], but not hand [61]. Data from a meta-analysis indicates higher circulating resistin in OA patients, particularly in males [62]. Although resistin is released from adipocytes in mice, in humans it is released from white adipose tissue-derived immune cells [63]. Consistent with this, resistin in both humans and mice plays a role in inflammation. Resistin is positively associated with both hand [64] and knee OA [65]. Another adipokine with an OA association is adiponectin; however, data is controversial. As previously stated, adiponectin, which plays a role in regulating glucose and fatty acid metabolism, is inversely associated with obesity; hence, OA should be associated with decreases in adiponectin. In accord, some clinical data supports that adiponectin plays a protective role in the prevention of cartilage damage associated with OA [66]. In these studies, circulating adiponectin levels are reported to be lower in OA patients compared with healthy individuals [67], with adiponectin being inversely related to knee OA severity [68] and high adiponectin decreasing the risk of hand OA severity [69]. In opposition, others demonstrate adiponectin is higher in OA patients compared with controls, and adiponectin is positively linked to increased OA severity [60, 70]. Some even demonstrate this positive association with knee OA [60]. Differences among adiponectin studies likely depend on whether groups were BMI dependent or independent.

Knee adipose: the infrapatellar fat pad (IFP)

As previously stated, obesity-induced OA risks are proposed to be due to both systemic and local effects of adipose tissue depots. An example of a weight-bearing joint with a local adipose depot is the knee. Specific to the knee environment, the infrapatellar fat pad (IFP), which is composed of adipocytes, immune cells, and blood vessels, is primed to participate in local inflammatory processes of the knee joint. It is now well established that the IFP is a source of local inflammatory mediators, including cytokines, adipokines, growth factors, free fatty acids and lipid mediators. These IFP-derived mediators have been recently reviewed [71–74]. Of note, most studies examining the IFP to date have relied on high fat diet-induced knee OA in mouse models or on IFP tissue collected from humans with end-stage OA undergoing total knee replacement surgery [75]. Understandingly, it is challenging for clinically-based human studies to be controlled for confounding variables, such as age or obesity status. Additionally, there is no defined gold standard for the measurement of obesity status, as different studies employ varying methodologies for assessing obesity including BMI, weight, WC, or dual-energy X-ray absorptiometry (DEXA) scanning [76]. Thus, our understanding of how the IFP contributes to the development and progression of OA is limited. In the context of obesity, we know even less about the contribution of the IFP to OA. Several excellent review papers, cited throughout this work, have been published highlighting the connection between obesity and OA and, more specifically, the IFP and OA. In the current manuscript, we sought to emphasize the latest studies that specifically focused on obesity when pursuing work involving the IFP and OA.

Anatomy/structure and proposed functions of the IFP

The knee joint is composed of many structures, including the distal femur, proximal tibia, patella and its tendon, cartilage, synovium, menisci, synovial fluid, fat pads, blood vessels, and nerves (Figure 1). The surrounding musculature provides structural support to this joint, as well. Fat pads that have been described in the knee joint include the IFP, the posterior knee fat pad, the quadriceps fat pad, and the pre-femoral fat pad [71]. Recently, the IFP has emerged as a key player to overall knee joint homeostasis, and there is evidence to support its role in the pathogenesis of knee joint OA [71–74, 77–82].

The IFP is the largest of the knee adipose depots and is found in the anterior part of the joint in the space shaped by the patella, femoral condyles, and tibial plateau (Figures 1 and 2). It attaches to the lower border of the inner non-articulating surface of the patella, to the intercondylar fossa of the femur, to the periosteum of the tibia, and the anterior part of the menisci. It sits behind the joint capsule, with its posterior surface coming into close contact with the synovium, and it is considered intracapsular but extrasynovial [71, 78]. Like all adipose connective tissue, the IFP is comprised of a network of adipocytes, fibroblasts, leukocytes (primarily macrophages and lymphocytes), and collagen matrix [71]. As such, it is poised to be a source of inflammatory mediators that contribute to OA, particularly under conditions

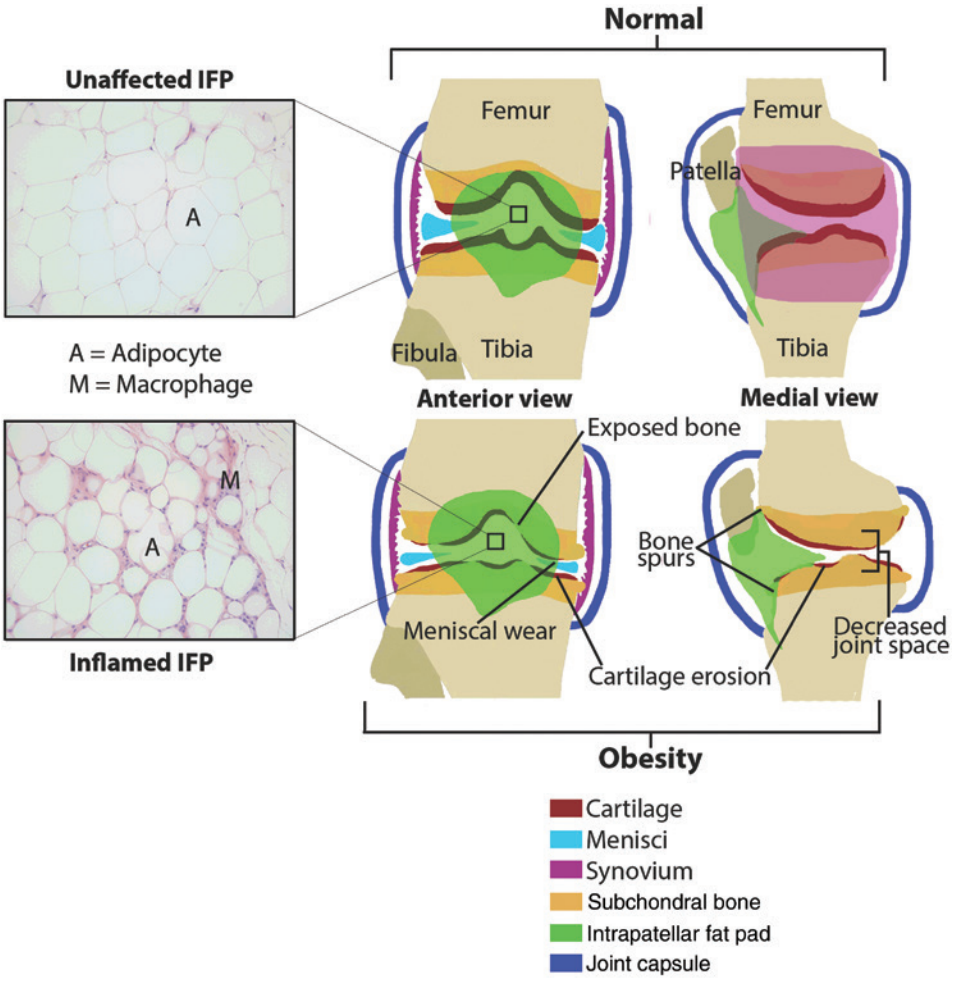

Figure 1: Representative images (anterior and medial views) of the intact knee organ under normal conditions where OA is not present (top aspect of figure) vs. OA in the context of obesity (bottom aspect of figure).
Insets to the left show histomicrographs (200× magnification) of IFP in lean vs. obese 5 month-old guinea pigs. Demonstrated changes associated with OA include: loss/erosion of cartilage, decreased joint space, meniscal wear, and exposed subchondral bone. Please note that, in the medial view of the obese knee, synovium (pictured in the medial view of the normal knee) has been removed to allow viewing of these OA-related changes. Finally, it should be emphasized that, while obesity is a primary risk factor for OA, obesity is not ubiquitous for OA to occur and lean individuals can also experience this disease. Image created for present publication by Josie Fouts with Adobe Photoshop (Adobe Systems Incorporated, San Jose, CA, USA).

induced by obesity (discussed below). Structurally, there is debate as to whether the IFP is more similar to subcutaneous adipose tissue [83] or visceral fat [73]. Branches of the genicular artery provide blood to the IFP and continue through this adipose depot to supply the patella [71]. Likewise, both the IFP and patella are innervated by branches of the saphenous, tibial, obturator, and recurrent and common peroneal nerves; hence, the IFP has been implicated as a potential source of pain in knee OA [78, 84].

Pathologies specific to the IFP include Hoffa disease, chondromas, nodular synovitis, and complications post-surgery. Hoffa's disease occurs when there is impingement of the IFP from the tibiofemoral or patellofemoral joints, resulting in pain, inflammation, and hyperplasia of the fat depot [85]. Chrondromas are mass lesions composed of bone and cartilage that usually arise within soft tissue adjacent to the joint. Their pathogenesis remains unknown but is thought to be due to metaplasia of para-articular tissues [86]. Nodular synovitis refers to thickening and inflammation of the synovium that lies adjacent to the posterior surface of the IFP [87].

The exact functions of the IFP are still not completely understood. The main role of the IFP is thought to be involved in facilitating distribution of synovial fluid across the knee joint, thereby providing lubrication [77–79]. It likely also provides shock absorbance from mechanical forces (similar to the menisci), knee joint stability, and may prevent instability and/or injury associated with loading

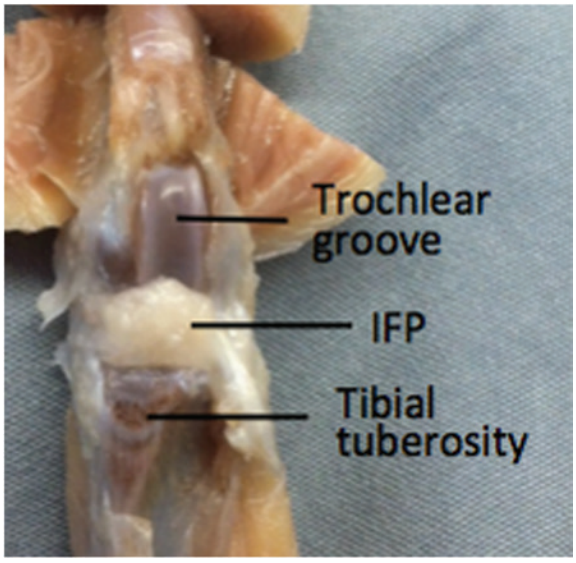

Figure 2: Representative gross image of the IFP from an obese 5-month-old guinea pig.
The joint capsule, synovium, and patella have been removed to allow exposure of this fat depot.

forces to the knee joint [79]. Ex vivo work performed on cadavers revealed that resection of the IFP decreased patellar rotation. From this study, the authors extrapolated that the IFP may play an important role in maintaining normal range of motion of the knee joint [88]. A more recent in vivo trial, however, whereby minimally invasive total knee arthroplasty was performed with or without removal of the IFP, found no significant differences in patellar tendon length, patellar complications, mean knee flexion, total Knee Society Score, and functional subscore between the two groups [89]. As limitations were acknowledged with this study, future projects utilizing live animal models may provide more information on how removal of the IFP affects normal joint motion.

Inflammatory cells and mediators of the IFP

Within the IFP, there are two main potential sources of inflammatory mediators: adipocytes and resident and infiltrating leukocytes, primarily macrophages and lymphocytes (Figure 3). Studies on how obesity influences the population of immune cells within the IFP have yielded conflicting results. A research abstract published by Chang et al. showed that IFP volume increased 54% without a concurrent infiltration of macrophages in mice fed a high-fat diet for 20 weeks [90]. However, visceral fat from the same mice showed an increase in both the overall volume (463% increase) and number of infiltrating macrophages, consistent with other studies in mice [91] and people [92]. Another study examining adipocyte cultured medium found a higher number of M2 macrophages in the culture medium from IFPs than subcutaneous fat obtained from end-stage OA patients [93]. These results suggest that the IFP is a distinct depot of white adipose tissue that may behave differently than other subcutaneous adipose tissue throughout the body.

Jedrzeczyk et al. [94] demonstrated increased numbers of adipocytes and infiltrating lymphocytes in IFPs from individuals with higher BMI. In concert with this, it has been shown that higher numbers of adipocytes in obese IFPs contribute to increased levels of cytokines, adipokines, and growth factors, such as TNFα, IL-6, leptin, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), in the knee joint [82, 95]. Another group, however, did not find correlations between fat pad volume and BMI or weight between control and OA patients, and instead found that IFP volume increased with age [96]. In a different study using a high fat diet-induced mouse model of knee OA [81], IFPs exhibited hypertrophy, increased macrophage infiltration, and increased gene and protein expression of several cytokines, adipokines, and growth factors compared to control mice on regular chow. IFPs from high fat diet-fed mice had increased gene expression of *VEGF*, *TNFα*, *TGFβ*, *Nampt*, and *leptin*. Levels of TNFα correlated with leptin, and the authors suggested that leptin may play a role in regulating *TNFα* expression in the IFP, as has been shown by others [97].

Additionally, IFPs from high fat diet-fed mice had higher mRNA expression levels of *lipocalin 2* and *chemerin*, two markers of adipocyte hypertrophy, compared with control mice [81]. Lipocalin 2 is a glycoprotein expressed by adipocytes, chondrocytes, and neutrophil granules. It has also been identified as a biomarker of cartilage degradation in guinea pig models of OA [98]. Chemerin is expressed by adipocytes and promotes calcium mobilization and chemotaxis of dendritic cells and macrophages [99]. Not only did IFPs from the high fat diet-fed mice demonstrate enhanced expression of numerous cytokines and growth factors, but chondrocytes from these mice exhibited increased apoptosis as measured by TUNEL assay [81]. The authors suggested that chemerin and lipocalin 2 may play important roles in regulating both immune responses in the IFP and chondrocyte apoptosis in the knee. The authors found no significant differences in plasma and IFP adiponectin levels between high fat diet and control diet mice, which may have been due to short

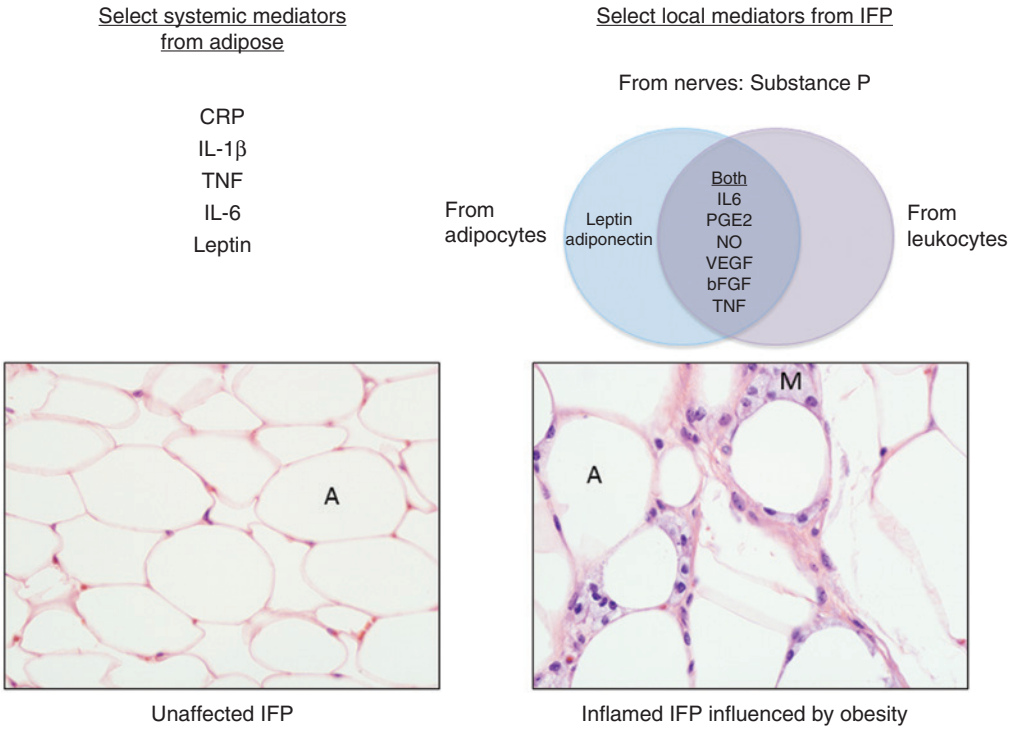

Figure 3: Select systemic (left) and local (right) mediators secreted from adipose tissue throughout the body and the IFP, respectively. Sources of mediators in the IFP have been divided into nerves, adipocytes, and leukocytes. Photomicrographs (500× magnification) of unaffected (left) and inflamed (right) IFP from lean vs. obese 5 month-old guinea pigs are shown. A, Adipocyte; M, macrophage. Image created in Powerpoint (Microsoft Windows, Redmond, WA, USA).

time course of the experimental design [81]. Adiponectin's role in development and progression of knee OA remains controversial, and may depend on which molecular form is present. In vitro studies show that adiponectin induces several destructive and inflammatory mediators including matrix metalloproteinases, IL-6, and inducible nitric oxide synthase [71]. Others have demonstrated an inverse relationship between synovial fluid adiponectin concentration and severity of knee OA, suggesting a possible protective role in OA [68].

A human study [100] demonstrated that IFP-derived adipocyte conditioned media had immunomodulatory effects on lymphocytes and macrophages. The conditioned media induced a pro-inflammatory response in T lymphocytes (increased proliferation and cytokine production). Macrophages treated with IFP-derived culture media displayed inhibited secretion of IL-12p40, and this effect was more pronounced with increasing adiposity. Additional studies showed that prostaglandin E2 (PGE2) and fatty acids (linoleic and oleic) were responsible for the inhibition of IL-12p40 secretion. The levels of these lipid mediators increased with increasing BMI of IFP donors, suggesting they might be responsible for the BMI-dependent inhibition of IL-12p40 secretion by macrophages [100]. The role of IL-12p40 in knee OA is not completely understood, as both pro- and anti-inflammatory effects have been described [101].

To compare cytokine gene expression and protein secretion in the knee joint, Distel et al. collected subcutaneous adipose tissue from the thigh and IFP tissue from obese women with knee OA [80]. Strikingly, IL-6 mRNA expression and protein secretion from the IFP was more than twice that of the subcutaneous thigh tissue. Protein secretion of soluble IL-6 receptor was 3.6-fold higher in the IFP than thigh subcutaneous fat tissue. No significant differences were noted in gene or protein expression for IL-1β, TNFα, IL-8, or macrophage chemotactic protein-1 (MCP-1). Compared to subcutaneous adipose tissue, gene expression of *leptin* in IFPs was decreased, with no difference in *adiponectin* expression. Protein secretion of leptin was 40% less while adiponectin secretion was 70% higher in IFPs compared to subcutaneous adipose tissue. Many genes involved with lipolysis and lipid uptake were also decreased in the IFP tissue. The authors suggested that the high IL-6 levels in the IFP may be responsible for the decreased expression of those genes involved with lipid metabolism, although a direct causal relationship has yet to be demonstrated. It has also been suggested that

adiponectin can induce IL-6 secretion by chondrocytes [102]. It remains unknown how the IFP from lean, healthy individuals contributes to overall knee joint homeostasis and if similar changes are present in lean individuals with knee OA compared to those who are obese.

Obesity, OA, and the size of the IFP

The size of the IFP, typically measured via area, volume or mass, is determined by a combination of hypertrophy of mature adipocytes, triglyceride synthesis and lipolysis, adipose stem cell-mediated adipogenesis, edema, fibrosis, and cellular infiltrate [74]. These dynamics vary according to fat pad location and developmental origin of the contributing cell population [103]. As it has been proposed that the volume and configuration of the IFP is important to knee function [104], several studies have attempted to verify if there are associations/correlations between the IFP size and knee OA, as well as to conclude whether BMI and/or weight influences IFP volume. It should be noted that included studies vary as to how IFP size is measured (usually depending on the primary outcome measure, such as MRI or histology), as well as whether adipose characteristics were distinguished in regards to adipocyte enlargement and/or number, cellular infiltrate, edema, and/or fibrosis.

To date, findings are conflicting as to the relationship between OA, obesity, and IFP size. Chuckpaiwong et al. [96] measured IFP volume via contrast enhanced MRI (three-dimensional T1-weighted) in lean controls without evidence of OA vs. overweight/obese patients with OA and did not find an association between IFP volume and BMI. Further analysis revealed that IFP volume was independent of pain and knee OA status. Instead, a significant positive relationship was found between subject age and IFP volume in the patients with OA. Han et al. performed a larger scale study utilizing contrast enhanced (two-dimensional T2-weighted) MRI and also found that IFP area (not volume) was significantly and positively associated with age, and not associated systemic fat mass, as measured by BMI. Further, IFP area was not associated with metabolic and inflammatory mediators, leptin, TNF, or IL-6, suggesting that IFP size may not be influenced by systemic metabolic inflammation. However, they did find consistent evidence that increased IFP area was associated with appropriate cartilage volume, as well as decreased cartilage defects, structural abnormalities of the joint (osteophytes and bone marrow lesions), and pain. Indeed, these findings were independent of a number of covariates, including body size and tibial bone area, suggesting that IFP area has a protective biomechanical role in knee OA, possibly by absorbing forces and reducing joint overloading.

Interestingly, animal studies also disagree as to how weight and/or obesity influences IFP size. Fu et al. [74] utilized barrier-raised and specific pathogen-free F344BN F1-hybrid rats to examine the relationship between aging and IFP mass. While this study was not designed to induce obesity in these rats, it did show that, as body weight increased throughout aging, IFP wet weight (not volume or area) decreased with age. Based on histology, this difference was not related to a change in adipocyte size nor relative stromal fraction area. The authors did, however, find that higher expression levels of both *TGFβ* and *Fn1*, pro-fibrotic and anti-adipogenic mediators, were associated with aging. Further, increased variation in adipocyte size during aging was noted. Collectively, the authors postulated that the decrease in IFP weight may be due to differences in adipogenesis and/or adipocyte cell death during aging. Of relevance, this study revealed a decrease in IFP mass as OA developed, which is opposite from the findings reported in Chuckpaiwong's human work, discussed above.

On the other hand, Iwata et al. [81] provided a high fat diet to C57BL/6J male mice to associate inflammation from the IFP with onset of knee OA. The total area of the IFP, determined via histology, was increased in the animals receiving the high fat diet compared to the control group. Histomorphometrical analyses revealed that total adipose area, individual adipocyte area, and active angiogenesis area of the IFP were positively correlated with osteophyte area. Increased macrophages were present in IFPs after 8 weeks on the dietary intervention, as well as enhanced mRNA expression levels of *VEGF*, *TNFα*, *leptin*, *Nampt*, and *TGFβ*. The authors conclude that adipocyte hypertrophy is linked to osteophyte formation via secretion of inflammatory cytokines and adipokines. Based on these publications, it may be necessary to tease out changes in IFP size strictly related to aging from those associated with diet-induced obesity.

Role of the IFP in knee pain

Pain is the most common symptom reported by patients with knee OA [105]. While the exact pathogenesis of knee pain in unclear, inflammation at the local level, at the dorsal root ganglia, and in the central nervous system have been implicated in OA-related pain [106]. In concert with the synovium and joint capsule, the IFP is a very sensitive structure that may contain part of the terminal sensory innervation for the knee, with a predominance of

small-sized substance P nerves compared to medium- or large-sized nerves [88, 107, 108]. The highest numbers of substance P nerves are located next to vessels [88]. Vasodilation follows release of substance P, allowing iterative extravasation of inflammatory cells and edema. If not resolved, edema can lead to soft tissue impingement, ischemia, and adipose tissue necrosis. In particular, anterior knee pain is thought to be associated with pathology of the IFP, and nociceptive stimulation of the IFP by injection of hypertonic saline supports this reasoning [109]. Further, numerous inflammatory and pain mediators promote the maintenance of inflammatory joint pain at the local level (such as nitric oxide and nerve growth factor) and by acting at receptors on dorsal root ganglia (including TNF, IL-6, calcitonin gene-related peptide, and vasoactive intestinal peptide), all of which may be exacerbated in obesity [106, 110, 111].

Two studies utilizing magnetic resonance imaging (MRI) have identified that the IFP is associated with pain in obese individuals. Hill et al. [112] found that synovitis in the IFP determined via conventional MRI was significantly correlated with pain change 15 and 30 months after baseline assessment. Using both conventional and contrast-enhanced MRI, Ballegaard et al. [113] demonstrated that severe inflammation in the IFP, as represented by contrast perfusion variables on dynamic MRI, was associated with severe pain. This study also found a significant correlation between MOAKS Hoffa-synovitis, a semi-quantitative score based on MRI-based hyperintensity in the IFP, and pain. Finally, a randomized controlled trial compared removal of the IFP vs. tissue sparing during minimally invasive total knee arthroplasty. While this study did not indicate the obesity status of the participants, those patient receiving complete IFP removal 1 year post-surgery still experienced anterior knee pain, while no evidence of pain was reported in the group that did not have this fat depot excised [89].

Returning to the consideration of IFP size and OA, increased IFP maximum area, as determined by contrast enhanced MRI, was associated with decreased knee pain when walking on a flat surface [72]. This is in contrast to Chuckpaiwong's study, mentioned above, which did not find an association between fat pad volume and WOMAC pain score.

Limitations of current studies and unanswered questions

Although the IFP represents a single player in the knee joint environment, it is emerging as an important tissue that likely plays a pivotal role in development and progression of knee OA in obesity. More studies are needed to characterize the IFP in lean, healthy people, as well as determine changes the IFP and knee joint undergo in both lean and obese individuals over time. As this review cites a relatively small number of human studies that vary in participant characteristics, study size, and outcome measures for the IFP, there is a need for additional work in animal models of OA to elucidate mechanisms whereby the IFP contributes to and/or damages joint homeostasis.

Perhaps the largest factor limiting the interpretation of findings related to the IFP is the paucity of information regarding the IFP in healthy individuals. Currently, samples are typically obtained post-mortem and do not necessarily reflect "normal" joint homeostasis [73]. Further, the question also remains whether the characteristics of the IFP vary in OA-prone vs. OA-resistant individuals, as both age and obesity are complicating factors in these analyses.

Determining the connection between obesity and OA, however, is also muddled by the fact that there is debate as to whether BMI and/or weight, which do not distinguish adipose from non-adipose tissue, are appropriate measures of metabolic triggered inflammation [114]. While BMI has been associated with decreased knee cartilage volume and thickness, as well as increased tibial bone area and knee cartilage defects [115, 116], work has shown that hip-to-waist ratio and WC, which are estimates of central adiposity, may be better predictors of OA incidence than BMI [114]. When possible, multiple measures of lean and fat body mass should be included in human studies.

A final consideration regarding obesity and OA addresses the biomechanical contribution of this disease in the context of metabolic inflammation. As discussed above, inflammation is a central component of a cyclical pattern involving obesity, OA, and physical inactivity [75]. Several recent studies suggest that metabolic inflammation and hyperlipidemia increase the susceptibility of chondrocytes to biomechanically-induced cellular stress, particularly after joint injury [117, 118]. While it is challenging, but perhaps not completely necessary, to isolate the inflammatory contribution of obesity to OA from the biomechanical contribution, future work should consider both aspects when assessing the role of the IFP in knee OA.

References

1. Health, United States, 2014: With Special Feature on Adults 55–64: Center for Disease Control and Prevention; 2014.

2. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating G. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011;377:557–67.
3. Denke MA, Sempos CT, Grundy SM. Excess body weight. An underrecognized contributor to high blood cholesterol levels in white American men. Arch Intern Med 1993;153:1093–103.
4. Ledoux M, Lambert J, Reeder BA, Despres JP. A comparative analysis of weight to height and waist to hip circumference indices as indicators of the presence of cardiovascular disease risk factors. Canadian Heart Health Surveys Research Group. Can Med Assoc J 1997;157 Suppl 1:S32–8.
5. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 1995;141: 1117–27.
6. Srinivasan SR, Bao W, Wattigney WA, Berenson GS. Adolescent overweight is associated with adult overweight and related multiple cardiovascular risk factors: the Bogalusa Heart Study. Metabolism 1996;45:235–40.
7. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997;46:701–10.
8. Reeves MJ, Newcomb PA, Remington PL, Marcus PM, MacKenzie WR. Body mass and breast cancer. Relationship between method of detection and stage of disease. Cancer 1996;77:301–7.
9. Secord AA, Hasselblad V, Von Gruenigen VE, Gehrig PA, Modesitt SC, Bae-Jump V, Havrilesky LJ. Body mass index and mortality in endometrial cancer: a systematic review and meta-analysis. Gynecol Oncol 2016;140:184–90.
10. Majumder K, Gupta A, Arora N, Singh PP, Singh S. Premorbid obesity and mortality in patients with pancreatic cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015 (in press).
11. Tan W, Gao M, Liu N, Zhang G, Xu T, Cui W. Body mass index and risk of gallbladder cancer: systematic review and meta-analysis of observational studies. Nutrients 2015;7:8321–34.
12. Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. Obes Rev 2015;16:1017–29.
13. Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, Kengne AP, Hercberg S, Czernichow S. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obes Rev 2011;12:653–9.
14. Hasegawa K, Tsugawa Y, Lopez BL, Smithline HA, Sullivan AF, Camargo CA, Jr. Body mass index and risk of hospitalization among adults presenting with asthma exacerbation to the emergency department. Ann Am Thorac Soc 2014;11:1439–44.
15. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med 1999;159:2582–8.
16. Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. Circulation 2005;111: 1992–8.
17. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–62.
18. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskelet Disord 2008;9:132.
19. Szoeke CE, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L. Factors affecting the prevalence of osteoarthritis in healthy middle-aged women: data from the longitudinal Melbourne Women's Midlife Health Project. Bone 2006;39:1149–55.
20. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. J Rheumatol 1993;20:331–5.
21. Gaudreault N, Maillette P, Coutu MF, Durand MJ, Hagemeister N, Hebert LJ. Work disability among workers with osteoarthritis of the knee: risks factors, assessment scales, and interventions. Int J Rehabil Res 2014;37:290–6.
22. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! Annals of the rheumatic diseases 2006;65:1403–5.
23. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, Zhao Y, Wang C. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291–7.
24. Jiang L, Rong J, Wang Y, Hu F, Bao C, Li X, Zhao Y. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2011;78:150–5.
25. Tepper S, Hochberg MC. Factors associated with hip osteoarthritis: data from the First National Health and Nutrition Examination Survey (NHANES-I). Am J Epidemiol 1993;137:1081–8.
26. Heliovaara M, Makela M, Impivaara O, Knekt P, Aromaa A, Sievers K. Association of overweight, trauma and workload with coxarthrosis. A health survey of 7,217 persons. Acta Orthop Scand 1993;64:513–8.
27. Andrianakos AA, Kontelis LK, Karamitsos DG, Aslanidis SI, Georgountzos AI, Kaziolas GO, Pantelidou KV, Vafiadou EV, Dantis PC, Group ES. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. J Rheumatol 2006;33:2507–13.
28. Ackerman IN, Osborne RH. Obesity and increased burden of hip and knee joint disease in Australia: results from a national survey. BMC Musculoskelet Disord 2012;13:254.
29. Reyes C, Garcia-Gil M, Elorza JM, Mendez-Boo L, Hermosilla E, Javaid MK, Cooper C, Diez-Perez A, Arden NK, Bolibar B, Ramos R, Prieto-Alhambra D. Socio-economic status and the risk of developing hand, hip or knee osteoarthritis: a region-wide ecological study. Osteoarthritis Cartilage 2015;23:1323–9.
30. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
31. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59:1207–13.

32. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger WH, Jr., Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004;50:1501–10.
33. Zhang W. Risk factors of knee osteoarthritis--excellent evidence but little has been done. Osteoarthritis Cartilage 2010;18:1–2.
34. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992;116:535–9.
35. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol 1994;139:119–29.
36. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10:161–6.
37. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyere O, Richette P, Cooper C, Chevalier X. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:851–9.
38. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, Akune T. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage 2012;20:1217–26.
39. Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. Osteoarthritis Cartilage 2012;20:614–21.
40. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev 2015;16:1–12.
41. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994;74:761–811.
42. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132–43.
43. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. J Obesity 2013;2013:291546.
44. Bilecik NA, Tuna S, Samanci N, Balci N, Akbas H. Prevalence of metabolic syndrome in women with rheumatoid arthritis and effective factors. Int J Clin Exp Med 2014;7:2258–65.
45. Lee CG, Lee JK, Kang YS, Shin S, Kim JH, Lim YJ, Koh MS, Lee JH, Kang HW. Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. Am J Gastroenterol 2015;110:310–9.
46. Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology (Oxford) 2015;54:588–600.
47. Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 2015;40:99–106.
48. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014;105:141–50.
49. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. J Endocrinol 2014;222:R113–27.
50. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, Pepys MB. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997;40:723–7.
51. Sharif M, Shepstone L, Elson CJ, Dieppe PA, Kirwan JR. Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee. Ann Rheum Dis 2000;59:71–4.
52. Hanna FS, Bell RJ, Cicuttini FM, Davison SL, Wluka AE, Davis SR. High sensitivity C-reactive protein is associated with lower tibial cartilage volume but not lower patella cartilage volume in healthy women at mid-life. Arthritis Res Ther 2008;10:R27.
53. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, Ding C. Circulating levels of IL-6 and TNF-alpha are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage 2010;18:1441–7.
54. Livshits G, Zhai G, Hart DJ, Kato BS, Wang H, Williams FM, Spector TD. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford Study. Arthritis Rheum 2009;60:2037–45.
55. Botha-Scheepers S, Watt I, Slagboom E, de Craen AJ, Meulenbelt I, Rosendaal FR, Breedveld FC, Huizinga TW, Kloppenburg M. Innate production of tumour necrosis factor alpha and interleukin 10 is associated with radiological progression of knee osteoarthritis. Annals Rheum Dis 2008;67:1165–9.
56. Berry PA, Jones SW, Cicuttini FM, Wluka AE, Maciewicz RA. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. Arthritis Rheum 2011;63:700–7.
57. Sierra-Honigmann MR, Nath AK, Murakami C, Garcia-Cardena G, Papapetropoulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ, Flores-Riveros JR. Biological action of leptin as an angiogenic factor. Science 1998;281:1683–6.
58. Stannus OP, Jones G, Quinn SJ, Cicuttini FM, Dore D, Ding C. The association between leptin, interleukin-6, and hip radiographic osteoarthritis in older people: a cross-sectional study. Arthritis Res Ther 2010;12:R95.
59. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, Jones G. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Annals Rheum Dis 2008;67:1256–61.
60. de Boer TN, van Spil WE, Huisman AM, Polak AA, Bijlsma JW, Lafeber FP, Mastbergen SC. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage 2012;20:846–53.
61. Massengale M, Reichmann WM, Losina E, Solomon DH, Katz JN. The relationship between hand osteoarthritis and serum leptin concentration in participants of the Third National Health and Nutrition Examination Survey. Arthritis Res Ther 2012;14:R132.
62. Li XC, Tian F, Wang F. Clinical significance of resistin expression in osteoarthritis: a meta-analysis. BioMed Res Int 2014;2014:208016.
63. Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, Bouloumie A. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 2006;49:744–7.

64. Choe JY, Bae J, Jung HY, Park SH, Lee HJ, Kim SK. Serum resistin level is associated with radiographic changes in hand osteoarthritis: cross-sectional study. Joint Bone Spine 2012;79:160–5.
65. Van Spil WE, Welsing PM, Kloppenburg M, Bierma-Zeinstra SM, Bijlsma JW, Mastbergen SC, Lafeber FP. Cross-sectional and predictive associations between plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. Osteoarthritis Cartilage 2012;20:1278–85.
66. Zheng S, Xu J, Xu S, Zhang M, Huang S, He F, Yang X, Xiao H, Zhang H, Ding C. Association between circulating adipokines, radiographic changes, and knee cartilage volume in patients with knee osteoarthritis. Scand J Rheumatol 2015 (in press).
67. Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jorgensen A, Tarp U, Hetland ML, Horslev-Petersen K, Hornung N, Poulsen JH, Flyvbjerg A, Stengaard-Pedersen K. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol 2009;36:1885–91.
68. Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res 2010;41:593–8.
69. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G, Middeldorp S, Huizinga TW, Kloppenburg M. Association between weight or body mass index and hand osteoarthritis: a systematic review. Annals Rheum Dis 2010;69:761–5.
70. Koskinen A, Juslin S, Nieminen R, Moilanen T, Vuolteenaho K, Moilanen E. Adiponectin associates with markers of cartilage degradation in osteoarthritis and induces production of pro-inflammatory and catabolic factors through mitogen-activated protein kinase pathways. Arthritis Res Ther 2011;13:R184.
71. Clockaerts S, Bastiaansen-Jenniskens YM, Runhaar J, Van Osch GJ, Van Offel JF, Verhaar JA, De Clerck LS, Somville J. The infrapatellar fat pad should be considered as an active osteoarthritic joint tissue: a narrative review. Osteoarthritis Cartilage 2010;18:876–82.
72. Han W, Cai S, Liu Z, Jin X, Wang X, Antony B, Cao Y, Aitken D, Cicuttini F, Jones G, Ding C. Infrapatellar fat pad in the knee: is local fat good or bad for knee osteoarthritis? Arthritis Res Ther 2014;16:R145.
73. Ioan-Facsinay A, Kloppenburg M. An emerging player in knee osteoarthritis: the infrapatellar fat pad. Arthritis Res Ther 2013;15:225.
74. Fu Y, Huebner JL, Kraus VB, Griffin TM. Effect of aging on adipose tissue inflammation in the knee joints of F344BN rats. J Gerontol A Biol Sci Med Sci 2015.
75. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. Pathobiol Aging Age Relat Dis 2012;2:17470.
76. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008;16:232–40.
77. Bastiaansen-Jenniskens YM, Wei W, Feijt C, Waarsing JH, Verhaar JA, Zuurmond AM, Hanemaaijer R, Stoop R, van Osch GJ. Stimulation of fibrotic processes by the infrapatellar fat pad in cultured synoviocytes from patients with osteoarthritis: a possible role for prostaglandin f2alpha. Arthritis Rheum 2013;65:2070–80.
78. Van Beeck A, Clockaerts S, Somville J, Van Heeswijk JH, Van Glabbeek F, Bos PK, Reijman M. Does infrapatellar fat pad resection in total knee arthroplasty impair clinical outcome? A systematic review. Knee 2013;20:226–31.
79. Gierman LM, Wopereis S, van El B, Verheij ER, Werff-van der Vat BJ, Bastiaansen-Jenniskens YM, van Osch GJ, Kloppenburg M, Stojanovic-Susulic V, Huizinga TW, Zuurmond AM. Metabolic profiling reveals differences in concentrations of oxylipins and fatty acids secreted by the infrapatellar fat pad of donors with end-stage osteoarthritis and normal donors. Arthritis Rheum 2013;65:2606–14.
80. Distel E, Cadoudal T, Durant S, Poignard A, Chevalier X, Benelli C. The infrapatellar fat pad in knee osteoarthritis: an important source of interleukin-6 and its soluble receptor. Arthritis Rheum 2009;60:3374–7.
81. Iwata M, Ochi H, Hara Y, Tagawa M, Koga D, Okawa A, Asou Y. Initial responses of articular tissues in a murine high-fat diet-induced osteoarthritis model: pivotal role of the IPFP as a cytokine fountain. PloS one 2013;8:e60706.
82. Ushiyama T, Chano T, Inoue K, Matsusue Y. Cytokine production in the infrapatellar fat pad: another source of cytokines in knee synovial fluids. Ann Rheum Dis 2003;62:108–12.
83. Vahlensieck M, Linneborn G, Schild H, Schmidt HM. Hoffa's recess: incidence, morphology and differential diagnosis of the globular-shaped cleft in the infrapatellar fat pad of the knee on MRI and cadaver dissections. Eur Radiol 2002;12:90–3.
84. Gardner E. The innervation of the knee joint. Anat Rec 1948;101:109–30.
85. Dragoo JL, Johnson C, McConnell J. Evaluation and treatment of disorders of the infrapatellar fat pad. Sports Med 2012;42: 51–67.
86. Rizzello G, Franceschi F, Meloni MC, Cristi E, Barnaba SA, Rabitti C, Denaro V. Para-articular osteochondroma of the knee. Arthroscopy 2007;23:910 e911–4.
87. Roemer FW, Jarraya M, Felson DT, Hayashi D, Crema MD, Loeuille D, Guermazi A. Magnetic resonance imaging of Hoffa's fat pad and relevance for osteoarthritis research: a narrative review. Osteoarthritis Cartilage 2015. [Epub ahead of print].
88. Bohnsack M, Wilharm A, Hurschler C, Ruhmann O, Stukenborg-Colsman C, Wirth CJ. Biomechanical and kinematic influences of a total infrapatellar fat pad resection on the knee. Am J Sports Med 2004;32:1873–80.
89. Pinsornsak P, Naratrikun K, Chumchuen S. The effect of infrapatellar fat pad excision on complications after minimally invasive TKA: a randomized controlled trial. Clin Orthop Relat Res 2014;472:695–701.
90. Chang W, DeMoe J, Kent C, Kovats S, Garteiser P, Doblas S, Towner R, Griffin T. 130 Infrapatellar fat pad hypertrophy without inflammation in a diet-induced mouse model of obesity and osteoarthritis. Osteoarthritis Cartilage 2011; 19:S66.
91. Mathis D. Immunological goings-on in visceral adipose tissue. Cell Metab 2013;17:851–9.
92. Duffaut C, Zakaroff-Girard A, Bourlier V, Decaunes P, Maumus M, Chiotasso P, Sengenes C, Lafontan M, Galitzky J, Bouloumie A. Interplay between human adipocytes and T lymphocytes in obesity: CCL20 as an adipochemokine and T lymphocytes as lipogenic modulators. Arterioscler Thromb Vasc Biol 2009;29:1608–14.

93. Bastiaansen-Jenniskens YM, Clockaerts S, Feijt C, Zuurmond AM, Stojanovic-Susulic V, Bridts C, de Clerck L, DeGroot J, Verhaar JA, Kloppenburg M, van Osch GJ. Infrapatellar fat pad of patients with end-stage osteoarthritis inhibits catabolic mediators in cartilage. Ann Rheum Dis 2012;71:288–94.
94. Jedrzejczyk T, Mikusek J, Rudnicki P, Lopata P. The infrapatellar adipose body in humans of various age groups. Folia Morphol 1996;55:51–5.
95. Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S, Mainard D, Netter P, Terlain B. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis Cartilage 2006;14:690–5.
96. Chuckpaiwong B, Charles HC, Kraus VB, Guilak F, Nunley JA. Age-associated increases in the size of the infrapatellar fat pad in knee osteoarthritis as measured by 3T MRI. J Orthop Res 2010;28:1149–54.
97. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM. Leptin regulates proinflammatory immune responses. FASEB J 1998;12:57–65.
98. Wilson R, Belluoccio D, Little CB, Fosang AJ, Bateman JF. Proteomic characterization of mouse cartilage degradation in vitro. Arthritis Rheum 2008;58:3120–31.
99. Wittamer V, Franssen JD, Vulcano M, Mirjolet JF, Le Poul E, Migeotte I, Brezillon S, Tyldesley R, Blanpain C, Detheux M, Mantovani A, Sozzani S, Vassart G, Parmentier M, Communi D. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med 2003;198:977–85.
100. Klein-Wieringa IR, Andersen SN, Kwekkeboom JC, Giera M, de Lange-Brokaar BJ, van Osch GJ, Zuurmond AM, Stojanovic-Susulic V, Nelissen RG, Pijl H, Huizinga TW, Kloppenburg M, Toes RE, Ioan-Facsinay A. Adipocytes modulate the phenotype of human macrophages through secreted lipids. J Immunol 2013;191:1356–63.
101. Cooper AM, Khader SA. IL-12p40: an inherently agonistic cytokine. Trends Immunol 2007;28:33–8.
102. Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, Gomez-Reino JJ, Gualillo O. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008;16:1101–9.
103. Wang L, Dai EL, Liu TY, Wang G, Shi LN. [Treating knee osteoarthritis by Chinese medicine and its correlation study with CT changes of infrapatellar fat pad]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2013;33:1494–9.
104. Saddik D, McNally EG, Richardson M. MRI of Hoffa's fat pad. Skeletal Radiol 2004;33:433–44.
105. Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, Song J, Cahue S, Chang A, Marshall M, Sharma L. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 2006;14:1033–40.
106. Sofat N, Ejindu V, Kiely P. What makes osteoarthritis painful? The evidence for local and central pain processing. Rheumatology 2011;50:2157–65.
107. Dye SF, Vaupel GL, Dye CC. Conscious neurosensory mapping of the internal structures of the human knee without intraarticular anesthesia. Am J Sports Med 1998;26:773–7.
108. Lehner B, Koeck FX, Capellino S, Schubert TE, Hofbauer R, Straub RH. Preponderance of sensory versus sympathetic nerve fibers and increased cellularity in the infrapatellar fat pad in anterior knee pain patients after primary arthroplasty. J Orthop Res 2008;26:342–50.
109. Bennell K, Hodges P, Mellor R, Bexander C, Souvlis T. The nature of anterior knee pain following injection of hypertonic saline into the infrapatellar fat pad. J Orthop Res 2004;22:116–21.
110. Schaible HG, von Banchet GS, Boettger MK, Brauer R, Gajda M, Richter F, Hensellek S, Brenn D, Natura G. The role of proinflammatory cytokines in the generation and maintenance of joint pain. Ann N Y Acad Sci 2010;1193:60–9.
111. Schaible HG. [The role of TNF-alpha as pain mediator]. Z Rheumatol 2010;69:237–9.
112. Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, Gale D, Grainger A, Conaghan P, Felson DT. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007;66:1599–603.
113. Ballegaard C, Riis RG, Bliddal H, Christensen R, Henriksen M, Bartels EM, Lohmander LS, Hunter DJ, Bouert R, Boesen M. Knee pain and inflammation in the infrapatellar fat pad estimated by conventional and dynamic contrast-enhanced magnetic resonance imaging in obese patients with osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2014;22:933–40.
114. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis Cartilage 2015;23:22–30.
115. Ding C, Cicuttini F, Scott F, Boon C, Jones G. Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. Arthritis Rheum 2005;52:3918–27.
116. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, Jones G. Two-year prospective longitudinal study exploring the factors associated with change in femoral cartilage volume in a cohort largely without knee radiographic osteoarthritis. Osteoarthritis Cartilage 2008;16:443–9.
117. Mooney RA, Sampson ER, Lerea J, Rosier RN, Zuscik MJ. High-fat diet accelerates progression of osteoarthritis after meniscal/ligamentous injury. Arthritis Res Ther 2011;13:R198.
118. Aspden RM. Obesity punches above its weight in osteoarthritis. Nat Rev Rheumatol 2011;7:65–8.