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The role of fat and inflammation in the pathogenesis and management of osteoarthritis

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Abstract

OA is a complex disease involving mechanical, metabolic and inflammatory contributions to its aetiology. A key risk factor, obesity, is becoming an increasing focus of research due to its multiple potential impacts on OA incidence, progression and symptom severity. An increased load due to an increase in body mass has been well established as a mechanical contribution to the pathophysiology of OA. However, evidence of obesity-linked to OA in non-weight-bearing joints has implicated the biological role of adipose inflammation and metabolic abnormalities in OA. The identification of inflammatory mediators such as adipokines (adipose-derived molecules) in OA has further incriminated the role of adiposity. This narrative review aims to discuss the role of adipose-derived inflammation in OA, with a focus on the contrast between systemic and local adipose tissue, and potential treatment applications targeting the adipo-inflammatory aspects of the disease.

Key words: adipokines, inflammation, infrapatellar fat pad, obesity, osteoarthritis

Rheumatology key messages

- Increasing obesity/adiposity results in an environment of low-grade systemic inflammation that contributes to an increase in inflammation in OA.
- The infrapatellar fat pad behaves differently compared with other adipose tissues and stimulates local inflammation in OA.
- The emerging role of adipose-derived inflammation highlights potential therapeutic targets for OA disease modification.

REVIEW

Introduction

OA is a highly prevalent disease that is estimated to affect one in every eight adults and is a leading cause of chronic pain [1, 2]. It is one of the top contributors to global disability, with the knee being identified as one of the joints most commonly affected by OA [3]. Adding to the individual and societal burden of OA, current treatment options lack any approved disease-modifying solutions and are limited to analgesic therapies to maintain joint function, and at end stage, surgical joint replacement [4]. Traditionally defined as a result of wear and tear affecting cartilage, OA is now better understood as a more complex disease involving mechanical, biochemical and biological processes that affect the whole joint [5, 6]. Specifically, OA is defined by the Osteoarthritis Research Society International as a joint disorder with an initial manifestation of abnormal joint tissue metabolism followed by anatomical and/or physiological changes, including cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function [7].

OA has a multifactorial pathophysiology with mechanical, metabolic and inflammatory contributions to its aetiology and recognized risk factors such as reduced muscle strength, joint injury and obesity, among others [8, 9]. In particular, obesity is a prominent risk factor due to its increasing societal prevalence and because it potentially contributes not only to the mechanical aspect by means of increasing joint load, but also to the metabolic and inflammatory facets of the disease due to the role of fat as an endocrine organ secreting an array of pro-inflammatory mediators [10].

Increasingly, the role of inflammation in OA has become more clearly defined, with the identification of various soluble inflammatory mediators, such as cytokines, chemokines, adipokines and lipids associated with the

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Table 1 Summary of adipokines and the associated effects in OA

Adipokines	Associated effects in OA	Levels in OA patients	Association with pain
Adiponectin	Increase cartilage degradation [83] Increase in IFP *vs* subcutaneous fat [18, 20]	Higher in plasma *vs* SF	Increase plasma [84] Decrease SF [85]
Resistin	Increase SF infiltration [18] Increase synovial hypertrophy [18] Increase cartilage degradation [87] Correlated with bone marrow lesions [87]	Higher in plasma *vs* SF	Increase SF [86]
Leptin	Increase IGF-1 and TGF-β [88] Increase MMP-2 and MMP-9 [90] Increase cartilage degradation [91]	Higher in SF *vs* plasma	Increase SF, serum [85, 89]
Visfatin	Increase in the IFP *vs* subcutaneous fat [20] Increase cartilage degradation [91]	Higher in SF *vs* plasma	Increase SF [85]

IFP: infrapatellar fat pad.

pathophysiology of both the structural and symptomatic disease [6]. Histological examination has demonstrated complex inflammation in the synovium (synovitis) of the osteoarthritic joint that otherwise would be a thin layer of cells that are a source of hyaluronan and lubricin, key components of SF [11]. There is a significant association between the presence and severity of synovitis and associated joint effusion with both the incidence and progression of OA pain and structural pathology [11, 12]. A recent study demonstrated that despite being within the normal range, increasing levels of SF white blood cells are associated with increasing synovitis, cartilage loss and bone marrow lesions in patients with knee OA [13]. Increased levels of some cytokines, including IL-6 and IL-8 in serum and SF, have similarly been found in patients with OA [14–16]. Despite the sometimes unclear understanding of how these cytokines affect OA progression, it is generally accepted that they induce catabolic processes and inhibit anabolic processes in the joint [6]. Along with these traditional cytokines, a class of adipose-derived molecules called adipokines have also been increasingly found to be associated with OA (Table 1) [17, 18]. The potential role of adipocyte-derived signalling molecules, in particular, has stimulated investigations not only on the role of systemic adipose tissue but also to examine local articular adipose depots such as the infrapatellar fat pad (IFP) to further understand the role of adipose-derived inflammation in OA [19, 20].

In light of the increasing evidence, the aim of this narrative review is to discuss adipose-derived inflammation and its potential role in OA. Specifically, the role adipose-derived inflammation plays in the pathology of OA and the contrast between systemic and local adipose-derived inflammation is examined. Finally, emerging evidence surrounding potential treatment applications targeting the adipo-inflammatory aspects of OA will be considered.

Adipose tissue and its role in inflammation

Historically characterized as an inert tissue for energy storage, adipose tissue has since been described as the largest endocrine organ in the body, consisting of adipocytes, nerve tissue and immune cells [21]. The discovery of leptin, an adipose-derived inflammatory molecule, was the catalyst for the change in understanding of the inflammatory role played by adipose tissue [22]. Since then, significant strides have been made to implicate a variety of immune cells, including macrophages, T cells, B cells and neutrophils, in adipose-associated inflammation, which with increasing obesity results in an environment of low-grade systemic inflammation [23, 24].

Increasing amounts of adipose tissue affect the local and systemic populations of immune cells in terms of both quantity and cell types towards a more pro-inflammatory profile [24]. Within adipose tissue, this is characterized by the shift from alternatively activated macrophages (M2) in lean individuals to classically activated macrophages (M1) in the presence of obesity [25–28]. The M1 or M2 phenotypes of these adipose tissue macrophages are broadly classified as pro-inflammatory and anti-inflammatory, respectively, with the former known to produce higher levels of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, and the latter producing anti-inflammatory/pro-anabolic molecules such as IL-10, IGF-1 and TGF-β [25, 27, 28]. Adipose tissue macrophages are often found surrounding necrotic adipocytes, with the purpose of consuming adipocyte debris in a process similar to foreign body tissue reaction, forming what is known as crown-like structures that increase in number in obesity [29, 30].

Inflammatory differences in the subtypes of brown (mainly found at the interscapular regions and associated with energy expenditure), white (mainly subcutaneous, intramuscular and visceral fat associated with obesity) and beige (brown adipocytes within white adipose tissue; the most common type of brown tissue in adult humans) adipose tissue are affected by increasing adiposity [29, 31, 32]. In obese individuals, these differences include higher IL-6 production in brown adipose tissue associated with lower values of body fat percentages, and higher uncoupling protein-1 production in brown adipose tissue compared with white adipose tissue, with an association to lower values of BMI, body fat percentage

and fat weight [33]. Additionally, brown adipose tissue, in contrast to white, is thought to downregulate the inflammatory profile of macrophages [34]. The relation of adipose tissue to inflammation is complex given the effects of not only increasing obesity, but the distinct types of adipose tissue. The differences in inflammatory profile between adipose tissue types have the capacity to differentially drive systemic and local inflammation through the accumulation and release of immune cells and inflammatory molecules [35]. Furthermore, recent pre-clinical studies have demonstrated crosstalk between different adipose tissue deposits with varying sensitivities to obesity-associated inflammation and that removal of the most inflamed tissue can modify the response of the remainder [36].

Adipose tissue inflammation in OA

Systemic adipose-derived inflammation in OA

The pathophysiological association between obesity and OA may manifest through several mechanisms. While biomechanical factors play a role in weight-bearing joints through increased load, the established association of obesity to OA in non-weight-bearing joints, such as in the hand, implicates biochemical/biological mechanisms as a contributory factor [37]. Pre-clinical studies using a high-fat diet (HFD) to induce obesity have shed light on the mechanical *vs* biological/inflammatory contribution to OA risk and pathophysiology. While a HFD has been consistently demonstrated to increase body weight, fat mass and spontaneous or injury-induced OA in mice, a number of studies have shown that OA severity is not correlated with body weight or joint loading [38–42]. Rather, OA incidence and/or severity in these and other *in vivo* studies [43–46] is associated with systemic and local joint inflammation and adipokine and cytokine levels. Interestingly, however, while genetically altered leptin signalling resulted in profound obesity, this was not associated with altered serum cytokine levels or OA, suggesting increased fat mass alone is not disease-inducing [47]. The increased OA risk with a HFD-induced fat mass may be associated with additional factors such as altered levels of cholesterol [48], specific fatty acids and lipoproteins [49–51] and gut microbiota [52]. Additionally, recent studies using combinations of HFDs and unloading of the hind limbs suggest that specific aspects of OA pathology (cartilage fibrillation and osteophyte size) require both adiposity and joint loading, while others (joint inflammation, chondrocyte apoptosis) occur with obesity alone [43].

Clearly there is a complex interplay between biomechanical and both systemic and local biological effects of obesity and fat mass, as well as the initiating mechanisms of adiposity itself. The impact of these different pathways on the effect of obesity on OA may vary between joints. In load-bearing joints such as the knee, the association of obesity-related metabolic syndrome in OA patients is weakened when outcomes are adjusted for BMI, suggesting increased load as a result of obesity may play a greater role in the pathophysiology [53]. In contrast, inflammation might be expected to play a more important role than biomechanics in the association of obesity with hand OA documented in numerous populations and countries [37, 54–62]. However, a number of studies have failed to demonstrate an association between obesity and hand OA [63, 64] and, as with knee OA, indices of metabolic syndrome (other than hypertension) were not associated with hand OA after adjusting for BMI in a recent cohort study [65]. Furthermore, neither serum leptin levels, impaired blood glucose metabolism or type 2 diabetes were found to be associated with increased hand OA [66–68]. Together this may suggest a greater role for biomechanics in obesity-associated hand OA risk than previously thought and/or the biological effect of obesity locally in joint tissues is more important than the systemic metabolic derangement in OA pathophysiology.

Adipose tissue is recognized as an endocrine organ that secretes a large number of inflammatory mediators, including cytokines (IL-1, IL-6, IL-8, TNF-α) and adipokines (leptin, adiponectin, resistin, visfatin) [10]. In addition to OA, adipose-derived inflammation has been implicated in several other diseases, including RA, diabetes and IBD [69–71]. The increase of white adipose tissue in obesity is postulated to create a systemic environment of increased inflammation through the release of both cytokines and pro-inflammatory adipokines such as leptin and visfatin, all of which have been associated with OA [72–75]. The shift from M2 to M1 macrophage phenotypes in adiposity, as previously discussed, is also significant, as it would enhance M1 cytokine-driven cartilage degeneration and reduce the capacity for tissue repair and angiogenesis by M2 macrophage-derived factors [25, 76]. The role of macrophages and their differential activation in OA is complex, however, and while the loss of M2 activation has been associated with enhanced systemic inflammation following pan-macrophage depletion [77], M2 macrophages do not directly attenuate M1-driven cartilage catabolism [78], and TGF-β produced by M2 macrophages can shift from being anabolic to pro-catabolic with ageing and OA [79, 80].

Adipokines are soluble molecules that predominantly originate from adipocytes and have been associated with obesity-related and metabolically induced inflammation, both of which have also been implicated in OA (Table 1) [81, 82]. While there is some contradictory evidence, leptin has generally been accepted as a major mediator in the construct of obesity and OA. It has been suggested that leptin mediates anabolic processes by the induction of insulin-like growth factor-1 and TGF-β, but also the expression of catabolic factors such as MMP-2 and MMP-9 [88, 92]. Leptin also stimulates the expression of IL-6 and IL-8 in synovial fibroblasts, alters the secretion of TGF-β, osteocalcin and collagen type I in subchondral osteoblasts and decreases chondrogenesis while increasing osteogenesis in cartilage progenitor cells [90, 93–95]. In addition to leptin, increased adiponectin and resistin have been associated with OA. Adiponectin is postulated to correlate to cartilage matrix degradation due to a positive association with circulating cartilage oligomeric matrix

protein and increased MMP-3 [83]. However, adiponectin was found to be negatively associated with hand OA, with significantly lower levels in those with progression compared with those without [96]. Resistin, an adipokine that is variably reported to be increased in obese patients, was found to exacerbate adipose tissue inflammation and insulin resistance in mice and induce an arthritic-like condition with synovial leucocyte infiltration and synovial hypertrophy after intra-articular administration [18, 81, 97, 98]. Serum levels of resistin have been positively associated with cartilage defects and bone marrow lesions in clinical studies [87].

Localized joint inflammation and adipose tissue

While the preceding evidence creates a construct for adiposity, systemic inflammation, adipokines and OA pathophysiology, studies have also shown elevated resistin, adiponectin and leptin occurring in knee SF compared with serum, which suggests a local adipogenic driver of pathology closer to the joint as opposed to just low-grade systemic inflammation [99, 100]. The IFP is a local adipose depot adjacent to the synovium in the knee joint. The IFP has been previously described as having a biomechanical role that contributes to load bearing, but emerging evidence also suggests a biochemical/biological contribution to the aetiology of knee OA [19, 101, 102]. The IFP is suggested to be the patellar tendons' source of blood supply, contributing to a potential pain mechanism in the knee or perhaps specifically patella-femoral OA [19]. The role of obesity as a risk factor and the implication of adipokines as well as synovitis in the pathophysiology of OA discussed above, coupled with the intrasynovial location of the IFP, has created a potential knee OA pathophysiological construct that has become an increasing focus of research [20, 103] that is now also being investigated in other joints with an intra-articular fat deposit, such as the hip [104]. In recent years, various clinical and pre-clinical approaches have been used to investigate the relationship between inflammatory properties in the IFP and the signs, symptoms and structure of OA.

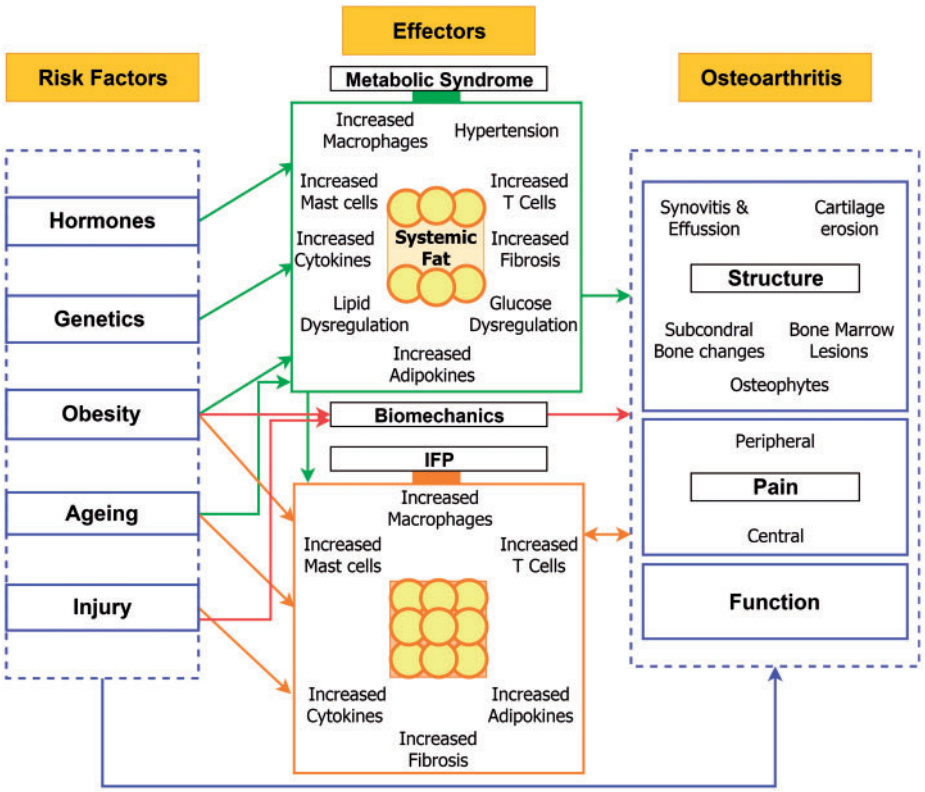
While it is a white adipose tissue, the IFP has been found to behave differently and demonstrate different characteristics compared with other adipose tissues in response to a HFD in the mouse [45, 105–107]. In addition to the development of OA features in these HFD models, an increase in total volume, adipocyte size and blood vessels was found within the IFP [45, 105] as occurs in systemic fat deposits [106]. The increased IFP volume was found in one study to be positively associated with osteophyte area [45]. While some studies have shown that a HFD increases the production of inflammatory cytokines, growth factors and adipokines in the IFP similar to systemic fat deposits [43, 45, 106], others have suggested the IFP is protected from obesity-driven inflammation despite concurrent OA induction [105]. Some of these changes observed in mice were also replicated clinically in end-stage knee OA patients, where the IFP differed significantly from other perisynovial adipose tissue with increased macrophages, toll-like receptor 4 expression and fibrosis in the latter, while both adipose tissues were influenced by BMI and showed an increase in adipocyte size and increased haematopoietic and M2 macrophage cell infiltration [108]. A recent clinical study in patients without OA found IFP volume to be positively associated with BMI [109]. This demonstrates sensitivity to diet/obesity-associated change in the IFP, but whether it is predictive of subsequent joint disease or is protective as previously suggested [110] remains to be determined.

While the role and effect of obesity on the IFP remains to be completely defined, IFP inflammation as identified by a change in MRI signal intensity has been linked to an increase in pain and correlated to radiographic abnormalities such as bone marrow lesions and cartilage defects in knee OA patients [111–114]. On a cellular level, the IFP, similar to surrounding synovial tissues in OA joints, has an increase in inflammatory cell types and markers indicative of a localized role in inflammation [115]. Within the IFP, pro-inflammatory phenotypes of T cells and macrophages were found to be the most abundant immune cells, and compared with subcutaneous adipose tissue, higher percentages of mast cells and lower percentages of T cells were detected in the IFP of OA joints [20]. Inflammatory molecules including IL-6, visfatin and adiponectin were also found in increased amounts in the IFP compared with subcutaneous fat [20, 103]. Additionally, new adipokines including serpin peptidase inhibitor clade E member 2, WNT1-inducible-signalling protein 2 and glycoprotein (transmembrane) NMB have been found to be produced by the IFP, with WNT1-inducible-signaling protein 2 increased in the OA IFP [116].

The increase in inflammatory cells and synthesis and secretion of pro-inflammatory factors by the IFP can not only directly drive pathological change in joint tissues such as cartilage, but may modify the phenotype of other cells in the joint, such as synovial fibroblasts [91, 117, 118]. The precise nature of the interaction between the IFP and surrounding tissues is not well defined. In *in vitro* studies using conditioned media and IFP and synovial fibroblast co-cultures have suggested the IFP contributes to synovial fibrosis through the release of one or more soluble factors [119], with IL-6 but not leptin or adiponectin implicated [120, 121]. In OA patients, adipokines involved in cartilage degradation, including leptin, chemerin and visfatin, are produced in both the synovial membrane and IFP [91]. Synovial fibroblasts produce an array of pro-inflammatory and pro-catabolic mediators when incubated with IFP, such as IL-8, IL-6, MMP-1 and MMP-3, and notably, these molecules were not produced in equivalent co-incubations with subcutaneous fat [117]. More recently, a similar composition of immune cell populations in the synovial membrane and IFP have been characterized, providing further evidence for an interactive environment involving the IFP in knee OA [122].

While the relationship between obesity and the IFP has been extensively investigated, as discussed earlier, the impact of the other well-recognized OA risk factors on

Fig. 1 A summary of the interaction between risk factors, systemic and local adipo-inflammatory pathways and biomechanics and the structural and clinical features of OA



IFP: infrapatellar fat pad.

the IFP, such as ageing and joint injury/trauma, has received less attention. In the rat, ageing has been associated with a decrease in IFP volume, increased IFP secretion of TNF-α and IL-13 and decreased expression of M2 macrophage genes [123]. Clinically, however, ageing has been linked to increasing IFP volume in OA but not normal joints [124], with increased IFP cross-sectional area beneficially associated with both radiographic and symptomatic OA [110, 125]. Trauma and injury have also been linked to abnormalities in the IFP, with evidence of fibrous changes with strenuous exercise, anterior cruciate ligament injury and after arthroscopy [126–128]. How the OA risk factors of ageing, injury and obesity interact to modify the IFP and its effects on joint homeostasis and pathology requires further investigation.

Adipo-derived inflammation and pain

The preceding discussion has largely focused on the relationship between adipose tissue/adiposity/obesity and OA structural pathology, but there are also potentially direct links with pain. The association between inflammation and OA pain is well established through the role of cytokines in the initiation and persistence of pain by directly activating nociceptive receptors in the joint [129–132]. Additionally, significant evidence implicates several pro-inflammatory molecules in peripheral and central sensitization [129–132]. More recently, studies investigating adipose-derived inflammation and pain have emerged. In upper extremity soft tissue disorders, visfatin and abdominal adiposity are associated with pain [133]. Furthermore, leptin and BMI were found to be positively associated with self-reported generalized body pain in otherwise healthy post-menopausal women as well as musculoskeletal pain in patients with FM [134].

Only a small number of studies have explored the association of adipokines to OA pain. Systemic adipokine levels (leptin and adiponectin) were associated with having an increased number of painful joints in women and positively correlated with pain [84, 89, 135]. Within the joint, levels of leptin, adiponectin and resistin in the SF were weakly correlated to patient-reported pain [86, 136]. However, a more recent and larger study showed pain was associated with intra-articular concentrations of various adipokines with joint-specific differences: high levels of visfatin and leptin in the hip and high levels of leptin and low levels of adiponectin in the knee [85]. Early data have also suggested no association between IFP-derived $CD4^+$ cells and pain [122]. While the inflammation and pain construct propose a natural role for adipokines/adipo-inflammation, the limited studies and conflicting evidence suggest a strong need for more well-designed studies.

Targeting adipose tissue in OA management

The above review clearly implicates the potential involvement of a number of systemic and local adipo-inflammatory pathways in OA structural and symptomatic disease, which are summarized in Fig. 1. While the precise role of different adipose tissues, specific adipose-derived mediators and biological versus mechanical effects of obesity and adiposity in OA onset and progression has yet to be fully resolved, therapeutic avenues have already begun to emerge. Numerous studies have established that weight reduction is beneficial to reducing OA symptoms [137–140], with persistent effects 1 year later even in the absence of weight loss maintenance [141], and reducing levels of inflammatory biomarkers with effects sustained at 24 months [142, 143]. Exercise and/or physical therapy even in the absence of significant weight loss has been shown to improve clinical outcome measures in OA patients [144, 145] and both symptoms and structure in pre-clinical animal models [40, 146, 147]. However, when directly compared, weight loss through diet or diet plus exercise results in superior clinical benefit compared with exercise alone [139], and conservative methods to target adiposity/obesity have therefore been incorporated into clinical guidelines for OA treatment [148].

The mechanism whereby weight loss improves OA symptoms is less clear. Some studies have demonstrated a dose-dependent reduction in cartilage damage/loss with weight loss [149, 150] while others have not [151], which may be associated with the larger absolute mass change in the former studies. Weight loss is associated with reduced joint loading, implicating biomechanics in the clinical improvement [152, 153]. However, patients in these studies also experienced reduced serum IL-6 and CRP in association with reduced fat mass but independent of body mass, indicating reduced inflammation may play a role [139, 154]. In a pre-clinical mouse study, reduced OA structural damage in exercised animals was not associated with changes in body mass, fat mass or serum cytokines, suggesting other mechanisms may be more important [40]. A recent study demonstrated that changes in adiposity and weight as a result of diet and exercise in patients were correlated to reduced IFP volume [155], potentially implicating this local joint tissue effect in the clinical improvement.

The unique inflammatory characteristics of different adipose tissues, their response to obesity and how these can be modified may provide distinct therapeutic targets for OA. There are a number of studies using genetically modified mice that have identified molecular pathways that regulate both obesity and its inflammatory/metabolic consequences. Ablation of micro-RNA (miR)-34a [156], MMP-19 [157], lecithin–cholesterol acyltransferase (Lcat) [51] and transient receptor potential vanilloid 4 (TRPV4) [158] all increased susceptibility to diet-induced obesity in mice. Evaluation of OA was only done in mice deficient in Lcat and TRPV4 and showed concurrently increased obesity and structural pathology, while mice deficient in apolipoprotein A-I had similar HFD-induced obesity to wild-type animals but significantly worse OA, suggesting a more direct role for high-density lipoprotein in the joint [51]. Decreased diet-induced obesity has been observed in mice with a deficiency in mast cells [159], ablation of steroid receptor RNA activator-1 [160] and overexpression of C1q/TNF-related protein-3 [161]. While none of these studies evaluated effects on OA, all reported decreased HFD-induced inflammatory cytokines such as IL-5, IL-6 and TNF. There is accumulating evidence from pre-clinical animal models, especially using genetically modified mice, that targeting specific inflammatory pathways can modify both post-traumatic and spontaneous age-associated OA (reviewed in [162–164]), but how this relates to changes in systemic or local adipose-inflammation has not been well explored. One study has demonstrated a key role for macrophage migration inhibitory factor in obesity-related white adipose tissue inflammation and metabolic syndrome despite no effect on adiposity itself [165]. An early pre-clinical study used dexamethasone to intervene in models of induced knee injury prior to the onset of OA, with results showing early improvements in the inflammation of the IFP that was not sustained at later time points and did not modify OA progression [166]. Mice deficient in sirtuin (Sirt)-6 were not more susceptible to HFD-induced obesity but did have worse OA associated with increased synovitis and IFP inflammatory cytokine expression [167]. Resveratrol, which activates Sirt-1, has been shown to significantly reduce HFD-induced OA pathology in mice in association with reducing serum leptin and IL-1β levels [168, 169].

There is great scope to therapeutically target the adipokines and inflammatory pathways that drive inflammation in the joint capsule, but to date there has been limited translation of the specific targets identified in pre-clinical studies to patients. Adiponectin and leptin have been postulated to be potential therapeutic targets, with suggestions of therapies likened to the anti-TNF-α treatments [170]. The use of a peroxisome proliferator-activated receptor gamma agonist has recently been suggested as a potential novel treatment in response to the finding that peroxisome proliferator-activated receptor gamma expression was lower in the IFP of obese OA patients [108]. Similarly increased activated macrophages and increased IL-1β associated with IFP activation and OA could be targeted by existing therapeutics in obesity-associated OA [118, 171–174]. With the emerging role of the IFP in knee OA, stratification of patients by MRI for locally applied intra-articular or even direct IFP injection of therapies may become a possibility.

Research gaps and future directions

While a great deal has been learned in recent years regarding the involvement of systemic and local adipose tissues in OA, there is still significant work to be done before therapeutics will be introduced into clinical practice. With regard to obesity itself, understanding the specific biomechanical, cellular and molecular pathways that link diet to adiposity and metabolic abnormalities and these to particular diseases such as OA is in its infancy.

In terms of systemic low-grade inflammation derived from adiposity, there is a need to define the key soluble signalling molecules (adipokines, cytokines, chemokines and growth factors), their specific joint targets and appropriate therapeutic approaches to target symptomatic and structural improvements in OA. Local to the knee joint, while existing research has implicated inflammation of the IFP in OA pathophysiology and symptoms, the detailed cellular and molecular mechanisms involved, the association between inflammation in the IFP and other synovial tissues, how these relate to clinical symptoms in patients and whether these can be measured by MRI or other non-invasive tools have not been well defined. The relationships between different risk factors for OA and the IFP and its role in structural and symptomatic disease have not been elucidated. While obesity and the IFP have been increasingly investigated, very few studies have explored the role of ageing and joint injury, and we found no studies have looked at the impact of hormones or genetics on the IFP. Furthermore, no studies, to our knowledge, have investigated OA in the novel concept of metabolically healthy obesity, where there is an absence of metabolic disorders in obese subjects, and such studies would be crucial when targeting obesity as a treatment. Finally, no studies to date have linked incident and progressive OA clinical symptoms or structural pathology in patients to the cellular and cytokine inflammatory profile of the IFP. This big-picture view of the inflammatory interaction between the IFP and the rest of the joint is needed to develop appropriate and patient and OA phenotype-specific diagnostic, prognostic and therapeutic approaches [30]. Continued research and well-designed studies are required in both the pre-clinical and clinical sectors before the existing knowledge described in this review can be applied in the clinical environment.

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