Adipose tissue inflammation : implications for joint diseases

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1 Introduction

1. OSTEOARTHRITIS

1.1 Introduction and epidemiology

Osteoarthritis (OA) is a musculoskeletal disorder of the joint (1). OA of the hand, knee, and hip can be classified according to the clinical criteria developed by the American College of Rheumatology (ACR)(2;3). The incidence of OA increases with age and is more common in women than in men (4;5). OA affects mainly the knee, hand, and hip (knee is 240/100 000, hand 100/100 000 and the hip 88/100 000 person-years (6)) and is usually progressive, although symptoms might remain stable for long periods of time (4;7).

1.2 Clinical features and risk factors

Disease onset of OA is multifactorial and risk factors for the occurrence of OA differ on the basis of the joints involved (Table 1). Clinically, OA presents with a heterogeneous phenotype, pain being the most predominant feature. It is mostly intermittent and increased during and after weight bearing activities (4;8). In addition, various other symptoms can be present as: joint stiffness, restriction of joint movement, sensation of instability or buckling of the joint. Crepitus, joint enlargement and deformities can be present by physical examination. All in all, these features can considerably affect the quality of life of patients (9).

Table 1. Risk factors for the occurrence and progression of osteoarthritis in knees and hands.

	Knee	**Hand**
Occurrence	Age, gender, physical activity, Body Mass Index, intense sport activities, quadriceps strength, bone density previous injury, vitamin D, smoking (protective or deleterious), hormone replacement therapy (protective), malalignment (including varus and valgus), genetics	Age, grip strength, activities, genetics occupation, intense sport
Progression	Age, Body Mass Index, vitamin D, hormone replacement therapy (protective), malalignment (including varus and valgus), chronic joint effusion, synovitis, intense sport activities, subchondral bone edema on MRI, genetics BMLs, meniscal lesions	Unknown

(adopted from Bijlsma et al. the Lancet, 2011)

1.3 Pathophysiology

One of the main features of OA is hyaline articular cartilage loss. Articular cartilage is composed of a specialized matrix of collagens, proteoglycans, and non-collagen proteins, in which chondrocytes constitute the unique cellular component (10). Although articular chondrocytes do not normally divide, they are assumed to maintain the extracellular matrix (ECM) by low-turnover replacement of certain matrix proteins

(10;11), which can be influenced by proteinases and ADAM-Ts (12). However, in OA this equilibrium appear disrupted and the rate of loss of collagens and proteoglycans from the matrix may exceed the rate of deposition of newly synthesized molecules, finally resulting in inappropriate articular cartilage and destruction of the joint (13).

As traditionally OA has been considered to be a non-inflammatory arthropathy, cartilage has long been the focus of attention in the pathophysiology of OA (5). However, cartilage is avascular and relies on adjacent tissues for nutrients and removal of products of chondrocytic metabolism. Furthermore, cartilage itself is aneural and longitudinal studies have suggested that cartilage loss and pain relief associate poorly, if at all (14;15). Although mechanopathology inevitably contributes to disease onset and progression, more recent evidence indicates additional roles for subchondral bone, ligaments, menisci, peri-articular muscle, capsule and synovium, contributing to the concept that in OA the whole synovial joint is affected (16-19).

An important structure related to OA is the synovial membrane. Cellular elements of the synovial membrane are a major source of components of synovial fluid. To help maintain the integrity of articular cartilage surfaces in joints, synovial lining cells in addition to chondrocytes, produce lubricin and hyaluronic acid (20). In patients with OA, concentrations and composition of these factors in synovial fluid are altered, adversely affecting the integrity of the cartilage (21;22). In addition, the synovium in patients with OA is also a source of matrix degrading enzymes, such as collagenases and aggrecanases, which could contribute to articular matrix degradation (23;24).

Although not as pronounced as in RA, it has become clear that inflammation is present in OA synovium (25). The most common histological findings are synovial lining and villous hyperplasia (16). Synovial infiltrates in OA can be characterized by infiltration of macrophages and lymphocytes either diffusely, or in peri-vascular aggregates (26;27). Initially, synovitis was assumed to occur primarily in association with fragments of cartilage and bone (detritus), but this was later shown to be an independent feature (28;29). Moreover, synovitis occurs both in early and late disease, but the presence of infiltrates appears to increase with advancing disease stage (16;30).

Several pathways and mediators appear to be involved in the development of synovitis (23). Matrix components and products released during cellular stress can activate danger-associated molecular pattern molecules (DAMPs) or the complement cascade, although their role in establishing OA is not fully understood (31-33). Upon these initial stimuli, activated innate immune cells produce proinflammatory cytokines and chemokines, IL-1

and TNFα being the most well studied, which could promote/maintain synovitis, cartilage degradation and contribute to infiltration of immune cells into the synovium (10).

Interestingly, synovitis associates with progression of cartilage erosion, although conflicting reports exist (30;34;35). Along these lines, joint pain and swelling have been shown to associate with synovial inflammation, implicating an important role of synovial inflammation in the pathophysiology of OA (23;26;36-38). The exact factors involved, or the sequence of events in the pathophysiology of OA are still not completely known, as structural joint damage in OA is a constant feature, but the clinical syndrome of OA is quite variable.

1.4 Disease progression

Radiographs of affected joints are used to monitor disease. Several grading systems exist, such as the Kellgren and Lawrence classification (39). This scoring system gives a composite score, which focuses on a sequence of osteophyte formation, joint space narrowing, and bone sclerosis and provides simple and practical ordinal scores for each joint (4). Similar to onset, disease progression is also multifactorial, as the progression rate varies per patient.

Structural disease progression is usually defined as increase in loss of joint space narrowing (radiography) or loss of cartilage (MRI) (Known risk factors for progression are shown in table 1) (40;41). Progression by radiography is determined by an increase in joint space narrowing above the smallest detectable change (42) and generally clinically significant changes in radiographic scores take at least 2 years (43;44). Although MRI is not the standardized method to assess progression, it provides an objective and a more sensitive assessment of morphology and integrity of articular cartilage and is a well established imaging method for identifying bone marrow and meniscal lesions (45;46).

2. RHEUMATOID ARTHRITIS

2.1 Introduction and epidemiology

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease and can be classified by the 1987 ACR criteria, and now more recently, by the revised 2010 classification criteria developed by the ACR and the European League Against Rheumatism (EULAR) (47;48). It is the most common inflammatory arthritis affecting approximately 0.5-1% of the adult population in Europe and Northern-America (49). The disease is more frequent in women than in men and the prevalence of onset increases with age (50).

2.2 Clinical features and risk factors

Classically RA is a poly-articular disease of the small joints of the hand and feet. The onset is gradual and can have intermittent or migratory joint involvement. Clinically predominant features are pain, stiffness and swelling of the joints (51). In addition, extra-articular manifestations have been described, such as: nodules, vasculitis, pericarditis, uveitis, rheumatoid lung, anemia, cardiovascular disease, fatigue and depression (50;52). Important diagnostic and prognostic markers for disease are the presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) (53-55).

Both genetic- and non-genetic risk factors have been described. The genetic contribution to RA is 50-60% and the strongest associating risk factors are the HLA-DRB1 "shared epitope" (HLA SE) alleles (56;57). These were shown to associate only with $ACPA^+$ disease (58). Thereby, the HLA SE alleles have been shown to bind and present citrullinated peptides (59;60). One of the strongest associating environmental factors described is smoking (61). Moreover smoking was shown to associate with citrullinated antigens in the bronchiolar alveolar fluid of the lungs and to interact with HLA SE genes in the predisposition to $ACPA^+$ RA (62;63). Together, these observations provide a possible link between gene-environment interactions in the pathogenesis of RA.

2.3 Pathophysiology

The exact cause of the disease and the reason for the joint specific localization in RA remains unknown. The combination of smoking and HLA SE positivity may trigger immunity to citrulline modified proteins (63). However, ACPAs can be detected in serum many years before onset of disease, implicating the involvement of other factors in the pathophysiology of RA (64;65). A secondary event could lead to a local innate immune response in the joint, resulting in neo-epitope formation. Activated $CD4^+$ T memory cells (directed against citrullinated proteins) accumulate in the synovium, and activate other cells such as monocytes, macrophages, and synoviocytes to secrete various soluble factors, such as: cytokines, chemokines and matrix metalloproteinases. In addition, these T cells can provide help to autoreactive B cells, which by autoantibody production could enhance and propagate the inflammatory processes. Progression of disease is characterized by synovial neovascularization and chronic hyperplasia, eventually leading to destruction of cartilage and bone (50).

2.4 Disease progression

Another important outcome measurement, in addition to other assessments of physical function and disease activity, is radiographic progression. As progression rates are

influenced by current therapies, radiographic progression reflects cumulative disease activity and is related to overall disability (66;67).

Disease progression on radiographs can be assessed amongst others, using the Sharp van der Heijde method. This method consists of a measure for cartilage degradation, the joint space narrowing and a component reflecting the amount of bone degradation, the erosion score (68;69). The presence of ACPA and/or RF are important determinants for a more severe disease progression, although various other (predisposing) genetic and environmental factors can also contribute (70-72).

3. OBESITY

3.1 Prevalence

The prevalence of obesity has increased dramatically in the Netherlands over the last decade. In 2009/2010, the prevalence of obesity was around 14% in the adult population, a twofold increase since the 1970s (Figure 1). Worldwide obesity has more than doubled since 1980 according to the world health organization (WHO). The prevalence of obesity differs per country, with the highest European prevalence in Greece, Ireland and the UK of around 26%. Worldwide the prevalence of obesity can go up to 36% (USA) (73;74). It is estimated by the International Association for the study of Obesity and the International Obesity Task Force (IASO/IOTF in 2010) that approximately 1.0 billion adults are currently overweight and a further 475 million adults are obese.

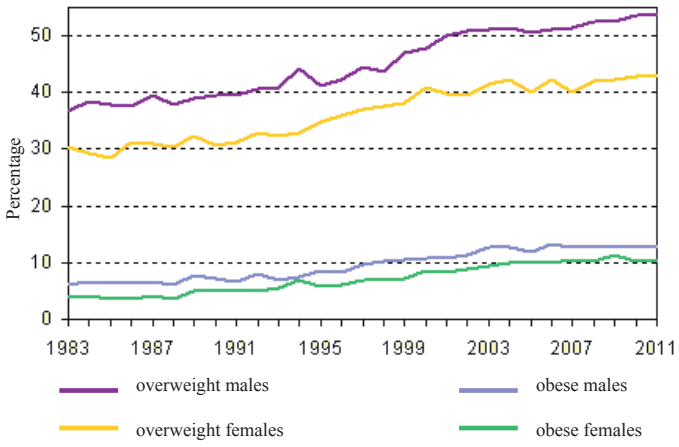

Figure 1. Percentage of overweight and obese adults in the Dutch population.
Percentage of Dutch population (adults ≥ 20years of age) who are overweight or obese in between 1983 and 2011, standardized for age and gender; *source RIVM, CBS statline*

The most widespread used method to assess excess body weight is by calculation of the Body Mass Index (BMI). The BMI is a very robust index for bodyweight in comparison to height; defined by the formula: weight (kg)/ height $(m)^2$. A normal bodyweight is usually defined as a BMI between 18-25 kg/m^2; overweight is defined as a BMI between 25-30 kg/m^2; and obesity is defined as a BMI> $30kg/m^2$. Obesity is strongly associated with a number of diseases, including insulin resistance, type 2 diabetes, atherosclerosis and ischemic heart disease, which influence life expectancy and have large economic and societal consequences (75). Intriguingly, obesity does not necessarily translate into increased risk for these co-morbidities, as up to 30% of obese individuals seem to be protected from obesity-related metabolic diseases and have been characterized to be 'metabolically healthy' (76-78).

3.2 Adipose tissue

Classically, adipose tissue has long been regarded as a long-term fuel reserve and provider for thermal insulation. During food deprivation, fuel reserves can be mobilized with the release of fatty acids for oxidation in other organs. In addition to fuel storage, adipose tissue also stores cholesterol and is involved in the metabolism of steroid hormones (79). In 1993, the first evidence for a functional link between obesity and inflammation was provided by increased adipose tissue expression of TNFα in murine models of diabetes and obesity (80). With the identification of the *ob*-gene and its protein

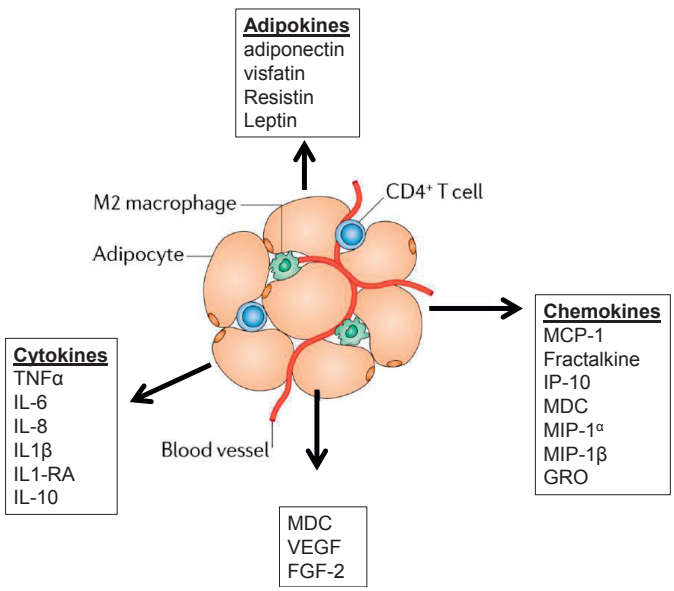

Figure 2. adipokine secretion by adipose tissue.
adapted from N. Ouchi et al. Nat. Rev. Immunol. 2011feb;11(21:85-97)

product leptin, shortly thereafter, it became increasingly evident that adipose tissue can function as an endocrine organ and is able to secrete many cytokines, collectively called adipokines, influencing whole body metabolism (Figure 2)(81;82). Up to date, many adipokines have been described. Among these, some of them, such as leptin, are considered to be proinflammatory, whereas others, such as adiponectin, have been described to have anti-inflammatory as well as proinflammatory properties depending on their molecular form (83).

3.3 Adipose tissue in obesity

Following the onset of obesity, the secretory status of an adipose tissue depot can be modified by changes in the cellular composition of the tissue, including alterations in the number, phenotype and localization of immune, vascular and strucural cells (84). Indeed, several studies in mice and men have shown that the immune cell composition differs per adipose tissue depot and varies with BMI (85-90). In addition, adipokine profiles differ per adipose tissue depot throughout the body (84;91;92). Although the functional importance of many of these individual adipose tissue depots remains unknown, recent evidence suggests that diet-induced changes in their adipokine secretion can influence the function of the associated tissue (84;93). Moreover, metabolic dysfunction of the adipose tissue in obesity may partly result from an imbalance in the expression of pro-and anti-inflammatory adipokines and could have a crucial role in the pathogenesis of obesity-related complications.

3.4 Adipose tissue immune cells

Besides adipocytes, adipose tissue is composed of various stromal cells, including: fibroblasts, progenitor cells, nerve cells, endothelial cells and immune cells (94;95). Macrophages and T cells are the most abundant immune cells in adipose tissue, but other cells, such as mast cells, NK cells and B cells have also been described (95). While the precise role of the immune cells in adipose tissue is largely unknown, there is increasing evidence of crosstalk between immune cells and adipocytes with both cell types able to influence each other (95). Indeed, studies in murine obesity have shown that macrophages not only infiltrate the adipose tissue in obesity, but also switch their phenotype from an anti-inflammatory towards a proinflammatory phenotype (96-98). Intriguingly, this phenotype switch has recently been attributed to an increase in macrophage lipid content (99). In humans, however, little is known about the influence of adipocytes on immune cells.

3.5 Obesity in OA

Obesity is a major risk factor for the development of knee OA, which has often been attributed to increased or altered mechanical load (100;101). However, mechanical

factors alone do not appear to be sufficient to explain the relationship between the incidence of OA and obesity, as obesity has also been shown to associate with OA of non-weight bearing joints (102;103). This is further supported by evidence obtained from murine studies linking obesity to increased/accelerated cartilage degeneration independently of body weight (104-106). Moreover, it has been shown in mice that the loss of body fat is more beneficial for symptomatic relief in knee OA than the loss of body weight (107). These studies imply a role for adipose tissue secreted factors, such as adipokines, in the pathophysiology of OA.

Sources for these adipokines could be systemic, derived from large adipose tissue depots as visceral fat, or more locally, derived from the depots residing in the bone marrow or in the knee joint (108-110). Indeed, differences in distribution of adipokines between the joint and the circulating compartment suggest that the joint is a unique area of activity for adipokines (111). It is therefore conceivable that adipokines secreted by local adipose tissue depots can potently influence joint homeostasis. Next to the potential effects of bone marrow adipose tissue in proximity of the joints, the body contains a unique joint-associated adipose tissue depot: the infrapatellar fat pad (IFP). The IFP is located intracapsularly and extrasynovially, in the vicinity of cartilage, synovium and bone. Little is known about its exact function, although it has been described as a facilitator of the distribution of synovial fluid and an absorber of forces through the knee joint (112). Furthermore the IFP has and been implicated to be a source of adipokines in the knee (108;112). Indeed, scarce information exists indicating the secretion of some adipokines, such as adiponectin, and IL-6 by the IFP (108;113;114). However, its immunological composition, secretory capacity and thereby its potential role in, or contribution to, joint inflammation in knee OA is still unknown.

3.6 Adipokines in OA

Among the adipokines described, several, such as leptin, adiponectin, resistin and visfatin have been implicated to have a role in the pathophysiology of OA.

Leptin levels are higher in synovial fluid (SF) compared to serum and leptin SF levels have been shown to correlate with BMI in patients with severe knee OA (115). The role of leptin however, appears controversial as both anabolic and catabolic functions of this adipokine have been described. Intra-articular injection of leptin has been shown to stimulate the synthesis of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β, on mRNA and protein level, indicating potential anabolic actions on cartilage metabolism (115). On the other hand, leptin has also been shown to increase the release of several matrix metalloproteinases and cytokines by chondrocytes (115-119) and concentrations of leptin in SF have been shown to correlate with the degree of

cartilage degeneration (120). Next to its effect on chondrocytes, leptin exerts direct modulatory effects on activation, proliferation, maturation, and production of inflammatory mediators in several immune cells, including lymphocytes, monocytes and macrophages, neutrophils and NK cells (83;121;122).

While plasma levels of adiponectin are increased in patients with OA, its role appears twofold. On the one hand, adiponectin might have a role in matrix degradation, by induction of proinflammatory mediators as IL-6, MMP-3, MMP-9 and MCP-1, but on the other hand might also be protective by up-regulation of tissue inhibitor of metalloproteinase-2 (TIMP-2) and inhibition of IL-1β induced MMP-13 expression in chondrocytes (123-125). It is noteworthy that this apparent contradiction also appears in vivo as SF adiponectin has been shown to correlate with severity of knee OA and aggrecan degradation (126;127), whereas high serum levels of adiponectin appear protective against progression of cartilage damage in hand OA (128). Therefore the exact role of adiponectin in OA remains to be determined.

The effects of visfatin and resistin in OA are less well described. Visfatin levels are increased in OA SF and correlate positively with degradation biomarkers of collagen type II and aggrecan, indicating that visfatin is involved in matrix degradation (129). Resistin has been shown to have direct proinflammatory effects on monocytes and macrophages and could induce arthritis upon intra-articular injection in mice (130;131). For those reasons, both adipokines appear to have proinflammatory effects on chondrocytes.

3.7 Obesity in RA

In addition to its association with OA, obesity has also been implicated to influence RA, as BMI was shown to negatively associate with radiographic progression in patients with early RA (132-134). Whether this is a protective effect of obesity against mechanisms involved in joint degradation in obesity or a reflection of joint damage at the time of first diagnosis remains unclear, as differences in joint damage between lean and obese patients have been observed at baseline (133). While the underlying mechanisms are unclear, adipose tissue secreted factors could play a role in the pathophysiological processes underlying RA.

3.8 Adipokines in RA

In patients with RA, concentrations of some adipokines, such as resistin and IL-6 have recently been shown to be elevated in serum and correlated to inflammatory markers as erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), and disease activity scores (DAS28) (135;136). Other adipokines, such as leptin have shown conflicting results and correlations between plasma concentrations of leptin and RA disease activity

are still debated (137-143). Moreover, certain publications describe serum leptin levels to be up-regulated in patients with RA, whereas others could not confirm this observation (135;137;144). Therefore the exact role and effects of leptin on inflammatory processes in the joint in patients with RA still needs further evaluation (145).

Studies regarding adiponectin point toward a proinflammatory role in RA (146;147). Locally, adiponectin could contribute to synovitis by up-regulation of proinflammatory cytokines and chemokines in RA synovial fibroblasts *in vitro* (147;148) even though key factors driving arthritis such as TNFα and IL-1β were not induced (147). In addition, plasma adiponectin levels were increased in patients with chronic versus early RA (149) and adiponectin levels associated with radiographic damage in longitudinal studies (146;150). Interestingly, human adiponectin consists of different isoforms, with different and sometimes counteracting functions (145;151;152). However, the role of total adiponectin, or the role of different adiponectin isoforms in disease progression remains to be determined.

Actions of resistin and visfatin in RA appear proinflammatory. Resistin levels are increased and correlate with markers of inflammation (111;153-155). Visfatin has been shown to induce proinflammatory cytokines and metalloproteinases in synovial fibroblasts (156;157). Moreover, inhibition of visfatin in CIA mice reduced arthritis (158) and associated with radiographic damage (146;150;159-161). However, for these and many other adipokines, the relationship with radiographic progression is still unknown.

4. OUTLINE OF THE THESIS

There were three main aims of this thesis:

1. To investigate the role of systemic adipose tissue secreted soluble mediators in radiographic progression in patients with RA and hand OA.
2. To characterize the IFP and to investigate its potential role in the joint in patients with knee OA.
3. Clinical implications.

This thesis is divided into three parts corresponding to the main aims.

Part one focuses on systemically secreted adipose tissue released soluble mediators and its effect on disease progression in patients with RA and hand OA (HOA). Obesity has been previously shown to modulate disease progression in patients with RA (132), which could imply a role for adipose tissue derived factors. Indeed, a few longitudinal

and cross-sectional studies have implicated a potential role for systemic adipokines in disease progression (130;146;150;159). However, the predictive value of circulating adipokines for disease progression over time is unknown. In **chapter 2** we therefore studied whether serum adipokine levels at baseline could affect disease progression. Adipokines in baseline serum samples from patients with early RA included in the Leiden Early Arthritis Cohort (EAC) were measured by luminex and levels were assessed for association with radiographic progression (increase in SvDH scores) over a period up to 4 years after inclusion. These studies revealed that baseline levels of adiponectin could strongly predict radiographic progression independently of the presence of anti-CCP antibodies. In contrast to these observations in patients with RA, previously, in patients with HOA, adiponectin has been shown to associate with a reduced radiographic progression (102). Adiponectin can exist in circulation in several isoforms with different immunomodulatory effects. Of these isoforms, high molecular weight adiponectin (hmwAPN) has been described as one of the most biologically active (162). Although both pro- and anti-inflammatory effects have been attributed to this isoform, its role in disease progression in patients with RA and in HOA remains unknown (151;163;164). Therefore in **chapter 3** we explored the possibility that the apparent opposing associations of adiponectin on disease progression in patients with RA and HOA are primarily mediated by the high molecular weight isoform. In this chapter baseline hmwAPN levels in serum (patients with HOA) or plasma (patients with RA) were determined by ELISA and their association with radiographic progression (5.6 years follow up in patients with HOA; 4 years follow up in patients with RA) was assessed. The patients with RA included in this study were participants in the EAC study and the patients with HOA were participants in the Genetic Arthrosis and Progression study (GARP).

Part two is dedicated to investigate and immunologically characterize the IFP, a joint-associated adipose tissue depot, in patients with end stage knee OA. The function of the IFP in the knee joint is relatively unknown, although scarce information exists indicating the secretion of some inflammatory mediators by the IFP (108;113;114). In addition, adipokines have been shown to be present in synovial fluid of in patient with OA (111). Because it is conceivable that soluble mediators secreted by the IFP could have a role in local inflammatory processes in the joint, we performed an extensive characterization of the IFP in **chapter 4**. IFP tissue samples and paired thigh subcutaneous adipose tissue samples (ScAT) were obtained from in patient with OA undergoing total knee replacement surgery. First, we studied the adipokines and cytokines secreted in fat-conditioned media by luminex and compared these to paired ScAT samples. Next, we compared the phenotype of adipocytes (by luminex) and the immune cell infiltrate (by flow cytometry) in these adipose tissues to gain more insight into the molecular nature of the effects observed.

Adipose tissue macrophages have been implicated to have a role in adipose tissue inflammation in obesity (98). Our studies in chapter 4 revealed macrophages to be the most abundant immune cell type in the IFP. In addition, we observed obesity-related changes in the phenotype of the IFP. Therefore, IFP-derived macrophages could have a role in the observed obesity-induced phenotypic changes of the IFP. For these reasons we obtained IFP from OA patients undergoing total knee replacement surgery and extensively characterized the phenotype of IFP-derived macrophages by flow cytometry in **chapter 5**.

The studies presented in this chapter revealed obesity-related phenotypic changes in IFP-derived macrophages. Because it is conceivable that macrophage-adipocyte crosstalk could underlie these observations, we explored in **chapter 6** the potential modulating effects of adipocytes on the phenotype of human macrophages *in vitro* and studied the possible molecular pathways involved. In these studies monocyte derived macrophages were cultured from healthy donors and co-incubated with adipocyte conditioned media (ACM) obtained from OA patients or patients undergoing elective aesthetic surgery. Cytokine release in culture medium was assessed by ELISA and phenotypic changes were studied by flow cytometry. To assess whether ACM-derived proteins or lipids were responsible for the effects observed, proteins and lipids were separated in ACM and their effects on macrophage cytokine release were studied. These studies revealed the modulatory effect to predominantly reside in the lipid fraction of ACM. Therefore, we identified the lipids in ACM by mass spectrometry and studied their effects on macrophage cytokine release after co-culture in an attempt to identify the lipids involved in the modulation observed.

Part three provides a pilot study to investigate the source of pain, one of the most predominant clinical features of knee OA. As the source of pain remains largely unknown, it is conceivable that inflammatory processes in synovium or the IFP could contribute to pain perception. For this reason we extensively characterized the immune cell populations in synovium and IFP by flow cytometry and correlated these populations to subjective measurements of pain in a unique cohort of patients with primary knee OA included in the GEneration of Models, Mechanism & Markers for Stratification of Osteo-Arthritis patieNts (GeMstoan) study (**Chapter 7**). **Chapter 8 and 9** provide a summary of the results and a discussion of the implications of the studies described in this thesis.

REFERENCE LIST

(1) Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiologic Clinics of North America 2004; 42(1):1-+.

(2) Altman RD. Criteria for the classification of osteoarthritis of the knee and hip. Scand J Rheumatol Suppl 1987; 65:31-39.

(3) Altman RD. Criteria for classification of clinical osteoarthritis. J Rheumatol Suppl 1991; 27:10-12.

(4) Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011; 377(9783):2115-2126.

(5) Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998; 41(8):1343-1355.

(6) Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995; 38(8):1134-1141.

(7) Kumm J, Tamm A, Lintrop M, Tamm A. The prevalence and progression of radiographic knee osteoarthritis over 6 years in a population-based cohort of middle-aged subjects. Rheumatol Int 2012; 32(11):3545-3550.

(8) Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am 2008; 34(3):531-559.

(9) Prevalence of disabilities and associated health conditions among adults—United States, 1999. MMWR Morb Mortal Wkly Rep 2001; 50(7):120-125.

(10) Goldring MB, Marcu KB. Cartilage homeostasis in health and rheumatic diseases. Arthritis Res Ther 2009; 11(3):224.

(11) Archer CW, Dowthwaite GP, Francis-West P. Development of synovial joints. Birth Defects Res C Embryo Today 2003; 69(2):144-155.

(12) Cawston T, Billington C, Cleaver C, Elliott S, Hui W, Koshy P et al. The regulation of MMPs and TIMPs in cartilage turnover. Ann N Y Acad Sci 1999; 878:120-129.

(13) Todhunter RJ, Fubini SL, Wootton JA, Lust G. Effect of methylprednisolone acetate on proteoglycan and collagen metabolism of articular cartilage explants. J Rheumatol 1996; 23(7):1207-1213.

(14) Felson DT, Goggins J, Niu JB, Zhang YQ, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis and Rheumatism 2004; 50(12):3904-3909.

(15) Bingham CO, III, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum 2006; 54(11):3494-3507.

(16) Oehler S, Neureiter D, Meyer-Scholten C, Aigner T. Subtyping of osteoarthritic synoviopathy. Clin Exp Rheumatol 2002; 20(5):633-640.

(17) Benjamin M, McGonagle D. Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. Arthritis Rheum 2007; 56(11):3601-3609.

(18) Hunter DJ, Felson DT. Osteoarthritis. BMJ 2006; 332(7542):639-642.

(19) Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis 2006; 65(10):1261-1264.

(20) Hui AY, McCarty WJ, Masuda K, Firestein GS, Sah RL. A systems biology approach to synovial joint lubrication in health, injury, and disease. Wiley Interdiscip Rev Syst Biol Med 2012; 4(1):15-37.

(21) STAFFORD CT, NIEDERMEIER W, HOLLEY HL, PIGMAN W. STUDIES ON THE CONCENTRATION AND INTRINSIC VISCOSITY OF HYALURONIC ACID IN SYNOVIAL FLUIDS OF

PATIENTS WITH RHEUMATIC DISEASES. Ann Rheum Dis 1964; 23:152-157.

(22) Dahl LB, Dahl IM, Engstrom-Laurent A, Granath K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. Ann Rheum Dis 1985; 44(12):817-822.

(23) Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012; 51(2):249-257.

(24) Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim Biophys Acta 2012; 1824(1):133-145.

(25) de Lange-Brokaar BJ, Ioan-Facsinay A, Van Osch GJ, Zuurmond AM, Schoones J, Toes RE et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthritis Cartilage 2012; 20(12):1484-1499.

(26) Scanzello CR, McKeon B, Swaim BH, DiCarlo E, Asomugha EU, Kanda V et al. Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship to symptoms. Arthritis Rheum 2011; 63(2):391-400.

(27) Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. Osteoarthritis Cartilage 2007; 15(5):516-523.

(28) Brandt KD. Pain, synovitis, and articular cartilage changes in osteoarthritis. Semin Arthritis Rheum 1989; 18(4 Suppl 2):77-80.

(29) Saito I, Koshino T, Nakashima K, Uesugi M, Saito T. Increased cellular infiltrate in inflammatory synovia of osteoarthritic knees. Osteoarthritis Cartilage 2002; 10(2):156-162.

(30) Krasnokutsky S, Belitskaya-Levy I, Bencardino J, Samuels J, Attur M, Regatte R et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. Arthritis Rheum 2011; 63(10):2983-2991.

(31) Happonen KE, Saxne T, Aspberg A, Morgelin M, Heinegard D, Blom AM. Regulation of complement by cartilage oligomeric matrix protein allows for a novel molecular diagnostic principle in rheumatoid arthritis. Arthritis Rheum 2010; 62(12):3574-3583.

(32) Sjoberg AP, Manderson GA, Morgelin M, Day AJ, Heinegard D, Blom AM. Short leucine-rich glycoproteins of the extracellular matrix display diverse patterns of complement interaction and activation. Mol Immunol 2009; 46(5):830-839.

(33) Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? Curr Opin Rheumatol 2008; 20(5):565-572.

(34) Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis — results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage 2005; 13(5):361-367.

(35) Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007; 66(12):1599-1603.

(36) Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 2006; 14(10):1033-1040.

(37) Baker K, Grainger A, Niu J, Clancy M, Guermazi A, Crema M et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann Rheum Dis 2010; 69(10):1779-1783.

(38) Roemer FW, Kassim JM, Guermazi A, Thomas M, Kiran A, Keen R et al. Anatomical distribution of synovitis in knee osteoarthritis and its association with joint effusion assessed on non-enhanced and contrast-enhanced MRI. Osteoarthritis Cartilage 2010; 18(10):1269-1274.

(39) KELLGREN JH, LAWRENCE JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16(4):494-502.

(40) Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H et al. Imaging in osteoarthritis. Rheum Dis Clin North Am 2008; 34(3):645-687.

(41) Ravaud P, Giraudeau B, Auleley GR, Chastang C, Poiraudeau S, Ayral X et al. Radiographic assessment of knee osteoarthritis: reproducibility and sensitivity to change. J Rheumatol 1996; 23(10):1756-1764.

(42) Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis 2005; 64(2):179-182.

(43) Boegard TL, Rudling O, Petersson IF, Jonsson K. Joint space width of the tibiofemoral and of the patellofemoral joint in chronic knee pain with or without radiographic osteoarthritis: a 2-year follow-up. Osteoarthritis Cartilage 2003; 11(5):370-376.

(44) Vignon E, Conrozier T, Hellio Le Graverand MP. Advances in radiographic imaging of progression of hip and knee osteoarthritis. J Rheumatol 2005; 32(6):1143-1145.

(45) Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfy C. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. Osteoarthritis Cartilage 2006; 14 Suppl A:A46-A75.

(46) Roemer FW, Nevitt MC, Felson DT, Niu J, Lynch JA, Crema MD et al. Predictive validity of within-grade scoring of longitudinal changes of MRI-based cartilage morphology and bone marrow lesion assessment in the tibio-femoral joint—the MOST study. Osteoarthritis Cartilage 2012; 20(11):1391-1398.

(47) Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31(3):315-324.

(48) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, III et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62(9):2569-2581.

(49) Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002; 4 Suppl 3:S265-S272.

(50) Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003; 2(6):473-488.

(51) Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet 2001; 358(9285):903-911.

(52) Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. Curr Med Res Opin 2008; 24(2):469-480.

(53) Visser H, Gelinck LB, Kampfraath AH, Breedveld FC, Hazes JM. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assays in rheumatoid arthritis. Ann Rheum Dis 1996; 55(3):157-161.

(54) Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000; 43(1):155-163.

(55) van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Toes RE, Huizinga TW. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. Arthritis Res Ther 2005; 7(5):R949-R958.

(56) Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987; 30(11):1205-1213.

(57) MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K et al. Characterizing the quantitative genetic contribution to

rheumatoid arthritis using data from twins. Arthritis Rheum 2000; 43(1):30-37.

(58) Huizinga TW, Amos CI, van der Helm-van Mil AH, Chen W, van Gaalen FA, Jawaheer D et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. Arthritis Rheum 2005; 52(11):3433-3438.

(59) Hill JA, Southwood S, Sette A, Jevnikar AM, Bell DA, Cairns E. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. J Immunol 2003; 171(2):538-541.

(60) Uysal H, Bockermann R, Nandakumar KS, Sehnert B, Bajtner E, Engstrom A et al. Structure and pathogenicity of antibodies specific for citrullinated collagen type II in experimental arthritis. J Exp Med 2009; 206(2):449-462.

(61) Karlson EW, Deane K. Environmental and gene-environment interactions and risk of rheumatoid arthritis. Rheum Dis Clin North Am 2012; 38(2):405-426.

(62) Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004; 50(10):3085-3092.

(63) Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006; 54(1):38-46.

(64) Nielen MM, van SD, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004; 50(2):380-386.

(65) Jorgensen KT, Wiik A, Pedersen M, Hedegaard CJ, Vestergaard BF, Gislefoss RE et al. Cytokines, autoantibodies and viral antibodies in premorbid and postdiagnostic sera from patients with rheumatoid arthritis: case-control study nested in a cohort of Norwegian blood donors. Ann Rheum Dis 2008; 67(6):860-866.

(66) Strand V, Sharp JT. Radiographic data from recent randomized controlled trials in rheumatoid arthritis: what have we learned? Arthritis Rheum 2003; 48(1):21-34.

(67) Bijlsma JW. Disease control with glucocorticoid therapy in rheumatoid arthritis. Rheumatology (Oxford) 2012; 51 Suppl 4:iv9-13.

(68) van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000; 27(1):261-263.

(69) van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999; 26(3):743-745.

(70) Kuhn KA, Kulik L, Tomooka B, Braschler KJ, Arend WP, Robinson WH et al. Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis. J Clin Invest 2006; 116(4):961-973.

(71) van GF, Ioan-Facsinay A, Huizinga TW, Toes RE. The devil in the details: the emerging role of anticitrulline autoimmunity in rheumatoid arthritis. J Immunol 2005; 175(9):5575-5580.

(72) van Gaalen FA, van AJ, Huizinga TW, Schreuder GM, Breedveld FC, Zanelli E et al. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum 2004; 50(7):2113-2121.

(73) Blokstra. RIVM nationaal compas, NL de maat. 2011.

Ref Type: Generic

(74) Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012; 307(5):491-497.

(75) Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444(7121):860-867.

(76) Bluher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes 2012; 19(5):341-346.

(77) Sims EA. Are there persons who are obese, but metabolically healthy? Metabolism 2001; 50(12):1499-1504.

(78) Calori G, Lattuada G, Piemonti L, Garancini MP, Ragogna F, Villa M et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. Diabetes Care 2011; 34(1):210-215.

(79) Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 2001; 60(3):329-339.

(80) Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose Expression of Tumor-Necrosis-Factor-Alpha - Direct Role in Obesity-Linked Insulin Resistance. Science 1993; 259(5091):87-91.

(81) Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372(6505):425-432.

(82) Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89(6):2548-2556.

(83) Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006; 6(10):772-783.

(84) Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011; 11(2):85-97.

(85) Bourlier V, Zakaroff-Girard A, Miranville A, De BS, Maumus M, Sengenes C et al. Remodeling phenotype of human subcutaneous adipose tissue macrophages. Circulation 2008; 117(6):806-815.

(86) Duffaut C, Zakaroff-Girard A, Bourlier V, Decaunes P, Maumus M, Chiotasso P et al. 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(10):1608-1614.

(87) Curat CA, Miranville A, Sengenes C, Diehl M, Tonus C, Busse R et al. From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. Diabetes 2004; 53(5):1285-1292.

(88) Kintscher U, Hartge M, Hess K, Foryst-Ludwig A, Clemenz M, Wabitsch M et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Arterioscler Thromb Vasc Biol 2008; 28(7):1304-1310.

(89) O'Rourke RW, Metcalf MD, White AE, Madala A, Winters BR, Maizlin II et al. Depot-specific differences in inflammatory mediators and a role for NK cells and IFN-gamma in inflammation in human adipose tissue. Int J Obes (Lond) 2009; 33(9):978-990.

(90) Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112(12):1796-1808.

(91) Samaras K, Botelho NK, Chisholm DJ, Lord RV. Subcutaneous and visceral adipose tissue gene expression of serum adipokines that predict type 2 diabetes. Obesity (Silver Spring) 2010; 18(5):884-889.

(92) Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998; 83(3):847-850.

(93) Takaoka M, Nagata D, Kihara S, Shimomura I, Kimura Y, Tabata Y et al. Periadventitial adipose tissue plays a critical role in vascular remodeling. Circ Res 2009; 105(9):906-911.

(94) Frayn KN, Karpe F, Fielding BA, Macdonald IA, Coppack SW. Integrative physiology of human adipose tissue. Int J Obes Relat Metab Disord 2003; 27(8):875-888.

(95) Anderson EK, Gutierrez DA, Hasty AH. Adipose tissue recruitment of leukocytes. Curr Opin Lipidol 2010; 21(3):172-177.

(96) Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; 117(1):175-184.

(97) Lumeng CN, Delproposto JB, Westcott DJ, Saltiel AR. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. Diabetes 2008; 57(12):3239-3246.

(98) Morris DL, Singer K, Lumeng CN. Adipose tissue macrophages: phenotypic plasticity and diversity in lean and obese states. Curr Opin Clin Nutr Metab Care 2011; 14(4):341-346.

(99) Prieur X, Mok CY, Velagapudi VR, Nunez V, Fuentes L, Montaner D et al. Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice. Diabetes 2011; 60(3):797-809.

(100) Felson DT, Chaisson CE. Understanding the relationship between body weight and osteoarthritis. Baillieres Clin Rheumatol 1997; 11(4):671-681.

(101) Berenbaum F, Sellam J. Obesity and osteoarthritis: what are the links? Joint Bone Spine 2008; 75(6):667-668.

(102) Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van OG et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010; 69(4):761-765.

(103) 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(2):119-129.

(104) Brunner AM, Henn CM, Drewniak EI, Lesieur-Brooks A, Machan J, Crisco JJ et al. High dietary fat and the development of osteoarthritis in a rabbit model. Osteoarthritis Cartilage 2012; 20(6):584-592.

(105) Louer CR, Furman BD, Huebner JL, Kraus VB, Olson SA, Guilak F. Diet-induced obesity significantly increases the severity of post-traumatic arthritis in mice. Arthritis Rheum 2012; 64(10):3220-3230.

(106) 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(6):R198.

(107) Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998; 25(11):2181-2186.

(108) 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(2):108-112.

(109) Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 2004; 145(5):2273-2282.

(110) Krings A, Rahman S, Huang S, Lu Y, Czernik PJ, Lecka-Czernik B. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. Bone 2012; 50(2):546-552.

(111) Schaffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Scholmerich J et al. Adipocytokines in synovial fluid. JAMA 2003; 290(13):1709-1710.

(112) Clockaerts S, Bastiaansen-Jenniskens YM, Runhaar J, Van Osch GJ, Van Offel JF, Verhaar JA et al. The infrapatellar fat pad should be considered as an active osteoarthritic joint tissue: a narrative review. Osteoarthritis Cartilage 2010.

(113) 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(11):3374-3377.

(114) Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S et al. Differential distri-

bution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis and Cartilage 2006; 14(7):690-695.

(115) Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003; 48(11):3118-3129.

(116) Otero M, Lago R, Gomez R, Lago F, Gomez-Reino JJ, Gualillo O. Phosphatidylinositol 3-kinase, MEK-1 and p38 mediate leptin/interferon-gamma synergistic NOS type II induction in chondrocytes. Life Sci 2007; 81(19-20):1452-1460.

(117) Koskinen A, Vuolteenaho K, Nieminen R, Moilanen T, Moilanen E. Leptin enhances MMP-1, MMP-3 and MMP-13 production in human osteoarthritic cartilage and correlates with MMP-1 and MMP-3 in synovial fluid from OA patients. Clin Exp Rheumatol 2011; 29(1):57-64.

(118) Gomez R, Scotece M, Conde J, Gomez-Reino JJ, Lago F, Gualillo O. Adiponectin and leptin increase IL-8 production in human chondrocytes. Ann Rheum Dis 2011; 70(11):2052-2054.

(119) Vuolteenaho K, Koskinen A, Kukkonen M, Nieminen R, Paivarinta U, Moilanen T et al. Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage—mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. Mediators Inflamm 2009; 2009:345838.

(120) Ku JH, Lee CK, Joo BS, An BM, Choi SH, Wang TH et al. Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. Clin Rheumatol 2009; 28(12):1431-1435.

(121) Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, Ng A et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A 1996; 93(25):14564-14568.

(122) Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 1998; 394(6696):897-901.

(123) Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and proinflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008; 16(9):1101-1109.

(124) Chen TH, Chen L, Hsieh MS, Chang CP, Chou DT, Tsai SH. Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta 2006; 1762(8):711-718.

(125) Kang EH, Lee YJ, Kim TK, Chang CB, Chung JH, Shin K et al. Adiponectin is a potential catabolic mediator in osteoarthritis cartilage. Arthritis Res Ther 2010; 12(6):R231.

(126) Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res 2010; 41(8):593-598.

(127) Hao D, Li M, Wu Z, Duan Y, Li D, Qiu G. Synovial fluid level of adiponectin correlated with levels of aggrecan degradation markers in osteoarthritis. Rheumatol Int 2011; 31(11):1433-1437.

(128) Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 2011; 70(7):1282-1284.

(129) Duan Y, Hao D, Li M, Wu Z, Li D, Yang X et al. Increased synovial fluid visfatin is positively linked to cartilage degradation biomarkers in osteoarthritis. Rheumatol Int 2012; 32(4):985-990.

(130) Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005; 174(9):5789-5795.

(131) Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the proinflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem

Biophys Res Commun 2005; 334(4):1092-1101.

(132) van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008; 67(6):769-774.

(133) Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007; 56(11):3575-3582.

(134) Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. Relation between body mass index and radiological progression in patients with rheumatoid arthritis. J Rheumatol 2003; 30(11):2350-2355.

(135) Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65(9):1198-1201.

(136) Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis 1993; 52(3):232-234.

(137) Anders HJ, Rihl M, Heufelder A, Loch O, Schattenkirchner M. Leptin serum levels are not correlated with disease activity in patients with rheumatoid arthritis. Metabolism 1999; 48(6):745-748.

(138) Hizmetli S, Kisa M, Gokalp N, Bakici MZ. Are plasma and synovial fluid leptin levels correlated with disease activity in rheumatoid arthritis ? Rheumatol Int 2007; 27(4):335-338.

(139) Palmer G, Gabay C. A role for leptin in rheumatic diseases? Ann Rheum Dis 2003; 62(10):913-915.

(140) Lee SW, Park MC, Park YB, Lee SK. Measurement of the serum leptin level could assist disease activity monitoring in rheumatoid arthritis. Rheumatol Int 2007; 27(6):537-540.

(141) Toussirot E, Nguyen NU, Dumoulin G, Aubin F, Cedoz JP, Wendling D. Relationship between growth hormone-IGF-I-IGFBP-3 axis and serum leptin levels with bone mass and body composition in patients with rheumatoid arthritis. Rheumatology (Oxford) 2005; 44(1):120-125.

(142) Bokarewa M, Bokarew D, Hultgren O, Tarkowski A. Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. Ann Rheum Dis 2003; 62(10):952-956.

(143) Seven A, Guzel S, Aslan M, Hamuryudan V. Serum and synovial fluid leptin levels and markers of inflammation in rheumatoid arthritis. Rheumatol Int 2009; 29(7):743-747.

(144) Wislowska M, Rok M, Jaszczyk B, Stepien K, Cicha M. Serum leptin in rheumatoid arthritis. Rheumatol Int 2007; 27(10):947-954.

(145) Neumann E, Frommer KW, Vasile M, Muller-Ladner U. Adipocytokines as driving forces in rheumatoid arthritis and related inflammatory diseases? Arthritis Rheum 2011; 63(5):1159-1169.

(146) Ebina K, Fukuhara A, Ando W, Hirao M, Koga T, Oshima K et al. Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. Clin Rheumatol 2009; 28(4):445-451.

(147) Ehling A, Schaffler A, Herfarth H, Tarner IH, Anders S, Distler O et al. The potential of adiponectin in driving arthritis. J Immunol 2006; 176(7):4468-4478.

(148) Frommer KW, Zimmermann B, Meier FM, Schroder D, Heil M, Schaffler A et al. Adiponectin-mediated changes in effector cells involved in the pathophysiology of rheumatoid arthritis. Arthritis Rheum 2010; 62(10):2886-2899.

(149) Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jorgensen A, Tarp U et al. 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(9):1885-1891.

(150) Giles JT, Allison M, Bingham CO, III, Scott WM, Jr., Bathon JM. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. Arthritis Rheum 2009; 61(9):1248-1256.

(151) Neumeier M, Weigert J, Schaffler A, Wehrwein G, Muller-Ladner U, Scholmerich J et al. Different effects of adiponectin isoforms in human monocytic cells. J Leukoc Biol 2006; 79(4):803-808.

(152) Tsao TS, Murrey HE, Hug C, Lee DH, Lodish HF. Oligomerization state-dependent activation of NF-kappa B signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30). J Biol Chem 2002; 277(33):29359-29362.

(153) Bo S, Gambino R, Pagani A, Guidi S, Gentile L, Cassader M et al. Relationships between human serum resistin, inflammatory markers and insulin resistance. Int J Obes (Lond) 2005; 29(11):1315-1320.

(154) Senolt L, Housa D, Vernerova Z, Jirasek T, Svobodova R, Veigl D et al. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. Ann Rheum Dis 2007; 66(4):458-463.

(155) Migita K, Maeda Y, Miyashita T, Kimura H, Nakamura M, Ishibashi H et al. The serum levels of resistin in rheumatoid arthritis patients. Clin Exp Rheumatol 2006; 24(6):698-701.

(156) Brentano F, Schorr O, Ospelt C, Stanczyk J, Gay RE, Gay S et al. Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. Arthritis Rheum 2007; 56(9):2829-2839.

(157) Busso N, Karababa M, Nobile M, Rolaz A, Van GF, Galli M et al. Pharmacological inhibition of nicotinamide phosphoribosyltransferase/visfatin enzymatic activity identifies a new inflammatory pathway linked to NAD. PLoS One 2008; 3(5):e2267.

(158) Evans L, Williams AS, Hayes AJ, Jones SA, Nowell M. Suppression of leukocyte infiltration and cartilage degradation by selective inhibition of pre-B cell colony-enhancing factor/visfatin/nicotinamide phosphoribosyltransferase: Apo866-mediated therapy in human fibroblasts and murine collagen-induced arthritis. Arthritis Rheum 2011; 63(7):1866-1877.

(159) Rho YH, Solus J, Sokka T, Oeser A, Chung CP, Gebretsadik T et al. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 2009; 60(7):1906-1914.

(160) Knudsen LS, Klarlund M, Skjodt H, Jensen T, Ostergaard M, Jensen KE et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome. J Rheumatol 2008; 35(7):1277-1287.

(161) Knudsen LS, Ostergaard M, Baslund B, Narvestad E, Petersen J, Nielsen HJ et al. Plasma IL-6, plasma VEGF, and serum YKL-40: relationship with disease activity and radiographic progression in rheumatoid arthritis patients treated with infliximab and methotrexate. Scand J Rheumatol 2006; 35(6):489-491.

(162) Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab 2007; 9(3):282-289.

(163) Tomizawa A, Hattori Y, Kasai K, Nakano Y. Adiponectin induces NF-kappaB activation that leads to suppression of cytokine-induced NF-kappaB activation in vascular endothelial cells: globular adiponectin vs. high molecular weight adiponectin. Diab Vasc Dis Res 2008; 5(2):123-127.

(164) Song H, Chan J, Rovin BH. Induction of chemokine expression by adiponectin in vitro is isoform dependent. Transl Res 2009; 154(1):18-26.