Adipokines as potential prognostic biomarkers in patients with acute knee injury

Stefan Kluzek, Nigel K. Arden & Julia Newton

Biomarkers

informa
healthcare

REVIEW ARTICLE

Adipokines as potential prognostic biomarkers in patients with acute knee injury

Stefan Kluzek[1]#, Nigel K. Arden[2,3], and Julia Newton[1]

[1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK, [2]Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK, and [3]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK

Abstract

This review considers adipokines as predictive biomarkers for early onset post-traumatic knee osteoarthritis (KOA). Serum concentrations of leptin and resistin can predict radiographic changes and are elevated in early KOA, with higher leptin concentrations independently associated with more severe knee changes. Plasma concentrations of resistin are chronically elevated after injury. Leptin, resistin, chemerin and vistfatin induce catabolic enzymes associated with cartilage degeneration. Available literature on adipokines in post-traumatic KOA pathogenesis suggests that they could contribute to risk prediction of early onset post-traumatic KOA. Further research is needed to further understand the association between adipokines, synovitis and long-term outcomes in this population.

Context

Adipokines are cytokines produced by white fat tissue in response to a positive energy balance determined by food intake. Obesity is a model of chronically elevated circulating levels of pro-inflammatory adipokines. The biomechanical aspects of increased body mass index (BMI) cannot explain the high incidence of osteoarthritis (OA) in the non-weight-bearing joints. Current concepts suggest that adipose tissue-derived cytokines can increase inflammatory responses to mechanical insults and result in fast progression to joint failure (Oliveria et al., 1999). This article will review current literature looking at the role of adipose tissue-associated inflammation in the pathogenesis of post-traumatic knee osteoarthritis (KOA) in the context of its impact on interactions between cartilage, synovium and subchondral bone.

Methods

A comprehensive search of electronic databases was carried out on Pubmed, the Cochrane Central Register of Controlled Trials, CINAHL and reference lists of relevant articles. The PubMed literature database was searched using MeSH index terminology. The following broad search terms were included: knee, post-traumatic and/or OA in combination with obesity, adipokine or adiponectin. This was complimented by a hand search of OA journals. This search was limited to human and animal studies in the English language. Limits to publication date applied between January 1985 and May 2014.

Systemic and local inflammation in post-traumatic knee osteoarthritis

Systemic inflammation measured by IL-6 has been shown to be an independent predictor of radiographic KOA in healthy, middle-aged British women (Livshits et al., 2009). Knee injury and obesity are strongly associated with the development of KOA (Anderson & Felson, 1988; Davis et al., 1989; Felson et al., 1988; Jiang et al., 2012; Lohmander et al., 2009; Roos, 2005). Blagojevic et al. have estimated, through a meta-analysis, that the overall pooled odd ratio (OR) for overweight and obese individuals is 2.63 (95% CI 2.28–3.05) and 3.86 (95% CI 2.61–5.70) (Blagojevic et al., 2010) for those with previous knee trauma. Obesity is characterized by high white adipose tissue (WAT) mass and associated with a state of chronic low-level inflammation. Anterior cruciate ligament (ACL) or meniscal injuries are among the strongest risk factors for early development of post-traumatic KOA (Englund et al., 2003; Neuman et al., 2008; Roos, 2005; von Porat, 2004). They represent a great model for the development of KOA, with well-defined early onset of disease. The incidence of all knee injuries is greatest in males under 30 years of age (Gianotti et al., 2009; Majewski et al., 2006). Joint injury may lead to a mild-to-moderate local

#Stefan Kluzek is responsible for design and analysis. E-mail: stefankluzek@doctors.net.uk

Address for correspondence: Dr. Stefan Kluzek, MBBS MRCP DipSEM MSc, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Headington, Oxford OX3 7LD, UK. E-mail: stefankluzek@doctors.net.uk

inflammatory reaction (Pessler et al., 2008) and inflamed knee synovium has been shown to be associated with more severe cartilage degeneration over the course of a year (Ayral et al., 2005). High systemic markers of inflammation have been previously reported in patients with knee trauma (Mendias et al., 2013).

Historically, the development of post-traumatic KOA in humans with ACL-deficient knees has been mainly attributed to recurrent episodes of knee instability. Primary ACL reconstruction, aimed at restoring mechanical stability, has not so far been proven to decrease the incidence of KOA or improve long-term function in cohort or randomised controlled studies (Barenius et al., 2014; Frobell et al., 2010, 2013; Lohmander et al., 2004; von Porat, 2004). It implies that another mechanism might be responsible for driving joint degeneration after initial trauma associated with instability.

Elevated BMI has been one of the strongest predictors of early KOA development after ACL and/or meniscal injuries, with an adjusted OR between 1.17 and 3.1 (Barenius et al., 2014; Kessler et al., 2008; Lebel et al., 2008; Li et al., 2011). Along with knee injury, other risk factors for the development of KOA, age and female gender, are also associated with increased systemic inflammation and a relatively higher percentage of fat tissue (Pirkola et al., 2010).

The proposed overlapping common mechanism is an adipose tissue-promoted inflammation. There is now increasing evidence that, at least in a subset of the patients, both inflammatory reactions of synovium and high adipokine concentrations may be prevalent causes of early deterioration of the knee joint (Guermazi et al., 2014; Karvonen-Gutierrez et al., 2014; Roemer et al., 2011; Sokolove & Lepus, 2013). In animal models, the effect of even extreme obesity on development of KOA is diminished in animals without a functional main adipokine pathway (Griffin et al., 2009).

Adipose tissue produces a series of chemicals that have been linked with the regulation of systemic and organ-specific inflammation, organ damage and chronic diseases like diabetes (Bozaoglu et al., 2007; Fantuzzi, 2005; MacDougald & Burant, 2007). It has been postulated that increased systemic inflammation and activity of organ-specific adipose stores promotes local inflammation. It has also been suggested that, on the joint level, this results in prolonged synovitis and affects the cartilage's ability to maintain an equilibrium between synthesis and degeneration of cartilage constituents (Bao et al., 2010; de Boer et al., 2012; Perruccio et al., 2014).

Signals from adipose tissue

Lipogenesis and lipolysis are two primary metabolic activities of WAT (Cristancho & Lazar, 2011). Both processes are regulated by endocrine and neural mechanisms. The discovery of the first adipose tissue hormone, leptin, and an increased interest in the endocrine functions of WAT have allowed for the identification of cytokines known collectively as adipokines (Ahima, 2006). The majority of these have been linked with lipid metabolism but also with inflammation. Adipokines associated with inflammation include classical pro-inflammatory agents (IL-6, TNF-α) and tissue specific agents such as leptin, adiponectin, Vaspin, Resistin, chemerin, visfatin and

adipsin. IL-6 produced by adipose tissue contributes to around a third of circulating IL-6 and is strongly associated with increasing obesity (Proenca et al., 2014).

Osteophytes are a structural hallmark of KOA and are associated with knee pain. Individuals with higher BMIs have an increased risk of fast cartilage loss (Roemer et al., 2009) and report more severe knee pain (Weiss, 2014). High ratio of fat mass to skeletal muscle mass is also positively associated with more severe KOA structural changes on magnetic resonance imaging (MRI) (Visser et al., 2014). Some adipokines have been linked with development of more severe knee changes (Karvonen-Gutierrez et al., 2014) and more painful KOA (Perruccio et al., 2014). Similarly, patients with a higher BMI are more likely to develop radiographic KOA after anterior crucial ligament reconstruction (Li et al., 2011). Secreted adipokines have also been shown to affect bone cell differentiation and can potentially impact on bone remodelling and bone formation (Bartell et al., 2011; Hamrick et al., 2004; Muruganandan et al., 2010, 2013). Moreover, bone marrow mesenchymal stem cells (MSCs) can differentiate, not only into bone forming osteoblasts, but also into adipocytes that can competitively suppress intracellular osteogenic signals (Muruganandan & Sinal, 2014).

Leptin

Leptin is a hormone that is produced in proportion to WAT mass and has been widely discussed in literature in the context of pro-inflammatory properties in OA. Its concentration is greater in women but it has not been entirely explained by either adipose load or sex hormone concentrations (Licinio et al., 1998). Apart from decreasing appetite, leptin promotes neutrophil mobilisation, cytotoxic lymphocyte and macrophage activation (Carbone et al., 2012). It also enhances production of MMP-1, MMP-3 and MMP-13 in human KOA cartilage (Koskinen et al., 2011), resulting in a progressive articular cartilage degeneration. The effect of leptin shows sex dimorphism in the association of its effect with KOA. Higher levels have been shown to be an independent predictor of MRI and radiographic knee changes associated with OA, but mainly in women.

Animal studies

Leptin has been shown to have both a strong anabolic and catabolic function in chondrocytes. The anabolic function occurs through the induction of IGF-1 and TGFβ1 synthesis (Dumond et al., 2003), while the catabolic function occurs by inducing MMP1 and MMP13 expression with a concomitant activation of STAT, MAPK, Akt and NF-κB signalling pathways (Hui et al., 2012). Diet-induced obesity in mice increases serum concentrations of leptin and KOA scores (Griffin et al., 2012). Moreover, extreme obesity in animals with impaired leptin signalling (leptin or leptin receptor deficient) does not cause increased incidence of KOA (Griffin et al., 2009). Leptin also affects bone metabolism and central injection (intra-cerebroventricular administration) leads to enhanced bone formation in a mutant leptin-deficient mouse model (ob/ob mice) (Bartell et al., 2011).

Human studies

Leptin receptors have been found to be expressed in articular chondrocytes (Figenschau et al., 2001) and modulate expression of canonical Wnt signalling receptors (Ohba et al., 2010). Synovial fluid (SF) and serum concentrations correlate with BMI in patients with established KOA, while SF/serum ratio is higher in early KOA (de Boer et al., 2012; Dumond et al., 2003; Staikos et al., 2013). Unlike other adipokines, leptin concentrations in SF are similar or higher than serum concentrations (Presle et al., 2006). Higher plasma concentrations have been associated with greater painful joint burden (Perruccio et al., 2014), with prevalent and incident KOA (OR 1.31, 95% CI 1.21–1.41), over a 10-year period in middle-aged women (Karvonen-Gutierrez et al., 2013). In a 5-year cohort study with very early-stage KOA, leptin has been shown to be associated with higher levels of systemic markers of synovial and cartilage metabolism and progression but not with the incidence of radiographic KOA (Van Spil et al., 2012). It has been cross-sectionally and longitudinally associated with reduced cartilage thickness (Stannus et al., 2013) and, interestingly, both obesity and female gender effects have mainly been related to leptin (Ding et al., 2008). Baseline levels have been associated with increased levels of bone formation biomarkers (over 2 years) in patients with established KOA (Berry et al., 2011). These have been correlated with larger osteophyte formation, synovitis and effusion on MRI (Karvonen-Gutierrez et al., 2014). Recently, in women, higher leptin has been associated with ~30% higher risk of having structural KOA (Karvonen-Gutierrez et al., 2012).

In summary, serum leptin levels have been positively linked with KOA on a molecular level and *in vivo*, both in animal models and human clinical studies. This review has not identified any studies looking at the role of leptin specifically in the development of post-traumatic KOA.

Adiponectin

This adipokine modulates insulin sensitivity and inflammation. It has been shown to have both anti- and pro-inflammatory properties, but its pivotal role is associated with an inhibitory effect of proinflammatory cytokines, such as tumour necrosis factor and interleukin-6 (IL-6). It is also associated with the induction of expression of anti-inflammatory proteins, including IL-10 and IL-1 receptor antagonist (Kumada et al., 2004; Tsatsanis et al., 2005; Wolf et al., 2004). Females have higher circulating levels of adiponectin than males (Combs et al., 2003). Visceral adipocytes are mainly responsible for adiponectin's systemic levels and, paradoxically, those are reduced in obesity (Arita et al., 2012). The transcription of adiponectin in adipocytes is suppressed by TNF and IL-6, which might explain the lower levels of serum adiponectin in obese individuals (Bruun et al., 2003; Fasshauer et al., 2003; Maeda et al., 2002). Two types of adiponectin receptor have been identified: AdipoR1, which mainly activates the AMPK phosphorylation pathway and AdipoR2, which is involved in the activation of PPAR-α (Lee et al., 2008).

Animal studies

Adiponectin is effective in reducing the activation of inflammatory pathways, including the NF-κB pathway (Lira et al., 2012). Diet-induced obesity has been shown to significantly increase the severity of post-traumatic KOA in a common inbred strain of laboratory mice. More importantly, levels of synovial inflammation in controlled uninjured knees inversely correlates with systemic levels of adiponectin (Louer et al., 2012).

Human studies

Adiponectin has not been detected in healthy cartilage and is up-regulated in patients with OA (Francin et al., 2014). It has been shown to be weakly associated with synovial inflammation in patients with end-stage KOA (de Boer et al., 2012). In human chondrocytes cultures, adiponectin induces MMP-3 (Tong et al., 2011). In patients with hand OA, high levels of adiponectin have been associated with a 70% reduction of joint space narrowing over a 6-year period (Yusuf et al., 2011). Development of early symptomatic KOA has been negatively associated with levels of adiponectin, and positively with high-sensitivity CRP (hs-CRP). Levels of adiponectin have not been shown to predict progression or incidence of radiographic KOA (Van Spil et al., 2012). Decreased levels in both plasma and SF have been shown to be lower in more advanced KOA, indicating that it may have a protective role (Honsawek & Chayanupatkul, 2010). Adiponectin has not been linked with an increase of bone formation biomarkers so far (Berry et al., 2011).

In summary, higher systemic concentrations of adiponectin probably protect against development of KOA in animal models, while some clinical human studies also confirm these properties. Despite this, adiponectin's role in the regulation of joint inflammation and cartilage homeostasis is still not clear.

Resistin

The adipocytokine resistin was initially investigated mainly as an insulin resistance inducing factor in mice (Steppan et al., 2001). The receptor for resistin is unknown, but it has strong pro-inflammatory properties and has been shown to trigger the release of other proinflammatory cytokines such as TNF- α, IL-1β and IL-6 (Bokarewa et al., 2005).

Human studies

Serum resistin is elevated in obese individuals (Degawa-Yamauchi, 2003) but this correlation is obscured in patients with advanced KOA (de Boer et al., 2012). In humans, resistin correlates better with subclinical inflammation than with insulin resistance (Steppan & Lazar, 2002). Resistin can be detected locally in the synovium of patients with KOA and correlates with histologically defined synovitis (de Boer et al., 2012). Both systemic and SF concentrations are elevated in post-traumatic knees and associated with the release of cytokines and cartilage degeneration (Lee et al., 2009). In a very early symptomatic KOA cohort, resistin levels have been shown to be positively associated with synovial biomarkers (sPIIINP) and high-sensitivity CRP but, more interestingly,

with the incidence of radiographic KOA (Van Spil et al., 2012). Such findings are independent of BMI and testing hs-CRP as a potential confounder in this association has suggested that those processes are independent.

Adipsin

Adipsin is involved in triglyceride metabolism but its effect on cartilage and the rest of the knee joint is not yet known, including any role in the modulation of synovitis after joint trauma. Higher adipsin levels have been found in obese individuals (Abu-Farha et al., 2014; Bienertova-Vasku et al., 2014). Lower serum concentrations of adipsin have been associated with greater painful joint burden in patients with end-stage hip and knee OA (Perruccio et al., 2014).

Chemerin

Chemerin is a novel adipokine that affects adipocyte differentiation and metabolism *in vitro* (MacDougald & Burant, 2007). It acts through G protein-coupled receptor: the chemokine like receptor-1 (CMKLR1, also known as ChemR23) and is expressed by circulating plasmacytoid dendritic cells, tissue-resident macrophages and adipocytes. It has been postulated that chemerin increases macrophage infiltration and activates a local inflammatory response (Goralski et al., 2007). Stimulating human chondrocytes with chemerin results in an increase in phosphorylation of Akt and a probable subsequent activation of MEK1/2. It also further activates the MAPK pathway and increases concentration of TNF-a, IL-1b, IL-6 and IL-8 (Berg et al., 2010). Along with this, it increases Toll-like receptor 4 mRNA and the synthesis of CCL2 in OA synoviocytes (Eisinger et al., 2012). The activated Toll-like receptor 4 leads to the development of an inflammatory reaction involving macrophages. CCL2 has been linked with mediating movement-related pain signalling in the animal model of post-traumatic KOA (Miller et al., 2012).

Animal studies

Mice bone marrow–derived osteoblast precursor cells differentiate to adipocytes when stimulated by chemerin (Muruganandan & Sinal, 2014). The increased bone mineralization with chemerin, in the CMKLR1 knockdown model, suggests that this signalling pathway acts, not only to promote adipogenesis, but also to actively suppress osteoblastogenesis.

Human studies

Chemerin has been associated with visceral obesity (Shin et al., 2012). High levels have been found to be associated with the activity of inflammatory arthritis (rheumatoid and psoriatic) (Ha et al., 2014; Xue et al., 2012). Chemerin is detected in SF and its higher concentrations are associated with KOA severity (Huang et al., 2012). SF levels of chemerin are similar in patients with KOA, rheumatoid and psoriatic arthritis (Valcamonica et al., 2014). Human chondrocyte cultures from patients with recent ACL injuries and end-stage KOA cells have been positive for both ChemR23 and chemerin staining (Berg et al., 2010). Stimulation of those cultures with chemerin has resulted in a significant elevation

of MMP-1, MMP-2, MMP-3, MMP-8 and MMP-13 levels, catabolic enzymes associated with cartilage degeneration.

Visfatin

Visfatin is called pre-B-cell colony-enhancing factor and is mainly produced by adipocytes in visceral fat and associated with increases in insulin resistance (Fukuhara et al., 2005). It regulates intracellular activity of the NAD-consuming enzymes affecting the production of inflammatory cytokines (TNFα, IL-6 and IL-1β) (Moschen et al., 2010). So far, no specific receptor has been identified, but it is thought that visfatin exerts proinflammatory action by regulating the insulin receptor pathway activity (Jacques et al., 2012). Human chondrocytes stimulated with visfatin induce synthesis of MMP-3 and MMP-13 (Gosset et al., 2008).

Human studies

Higher levels are observed in subjects with broader waists (Bienertova-Vasku et al., 2014) and associated with higher triglycerides but lower HDL (Abu-Farha et al., 2014). Patients with rheumatoid arthritis have higher serum levels of visfatin than healthy controls (Otero et al., 2006). Vistafin has been also shown to be produced and stored by synovial membrane, cartilage and the subchondral bone in patients with KOA (Laiguillon et al., 2014).

Summary

Animal research in this field, assessing the role of pro-inflammatory cytokines related to adipose tissue in the development of post-traumatic OA (PTOA), is very promising. Animals with impaired leptin pathways do not develop KOA, even in the presence of extreme obesity, indicating that increased loading cannot explain cartilage degeneration alone. Higher leptin levels have been associated with more severe progression of knee joint degeneration.

Leptin, resistin, chemerin and vistfatin have all been shown to induce chondrocyte production of matrix metalloproteinases. Based on the available literature on the involvement of adipokines in post-traumatic KOA pathogenesis, it is plausible that adipokines (especially leptin in women), resistin and chemerin (in men and women) may, in the future, contribute to a risk model of early development of KOA after ACL and/or meniscal injury. The relative activity of the various adipokines with respect to their effects on the synovium, bone and cartilage after knee trauma remains to be determined. Local changes in adipokine concentrations may have important pathophysiological implications for cartilage homeostasis but, so far, only leptin seems to correlate well with SF concentration and the systematic elevation of resistin levels has been proven to reflect SF concentration after joint injury.

This review identifies the need for prospective cohort studies to investigate the role of serum and SF adipokines as potential biomarkers for early post-traumatic OA in patients with acute ACL and/or meniscal injuries. Long-term follow-up will help to identify those at risk of a poor outcome and identify possible therapeutic targets in this pathway.

Declaration of interest

The authors declare no conflicts of interests. The authors alone are are responsible for the content and writing of this article.

References

Abu-Farha M, Behbehani K, Elkum N. (2014). Comprehensive analysis of circulating adipokines and hsCRP association with cardiovascular disease risk factors and metabolic syndrome in Arabs. Cardiovasc Diabetol 13:76.

Ahima RS. (2006). Adipose tissue as an endocrine organ. Obesity (Silver Spring) 14:242s–9s.

Anderson JJ, Felson DT. (1988). Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 128:179–89.

Arita Y, Kihara S, Ouchi N, et al. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 425:560–4.

Ayral X, Pickering EH, Woodworth TG, et al. (2005). Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis – results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthr Cartil 13:361–7.

Bao JP, Chen WP, Feng J, et al. (2010). Leptin plays a catabolic role on articular cartilage. Mol Biol Rep 37:3265–72.

Barenius B, Ponzer S, Shalabi A, et al. (2014). Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. Am J Sports Med 42:1049–57.

Bartell SM, Rayalam S, Ambati S, et al. (2011). Central (ICV) leptin injection increases bone formation, bone mineral density, muscle mass, serum IGF-1, and the expression of osteogenic genes in leptin-deficient ob/ob mice. J Bone Miner Res 26:1710–20.

Berg V, Sveinbjornsson B, Bendiksen S, et al. (2010). Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin(21-157). Arthritis Res Ther 12:R228.

Berry PA, Jones SW, Cicuttini FM, et al. (2011). Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. Arthritis Rheum 63:700–7.

Bienertova-Vasku J, Novak J, Zlamal F, et al. (2014). The prediction role of indexes of circulating adipokines for common anthropometric and nutritional characteristics of obesity in the obese Central European population. Eat Behav 15:244–51.

Blagojevic M, Jinks C, Jeffery A, Jordan KP. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthr Cartil/OARS, Osteoarthritis Res Soc 18:24–33.

Bokarewa M, Nagaev I, Dahlberg L, et al. (2005). Resistin, an adipokine with potent proinflammatory properties. J Immunol 174:5789–95.

Bozaoglu K, Bolton K, McMillan J, et al. (2007). Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 148:4687–94.

Bruun JM, Lihn AS, Verdich C, et al. (2003). Regulation of adiponectin by adipose tissue-derived cytokines: *in vivo* and *in vitro* investigations in humans. Am J Physiol Endocrinol Metab 285:E527–33.

Carbone F, La Rocca C, Matarese G. (2012). Immunological functions of leptin and adiponectin. Biochimie 94:2082–8.

Combs TP, Berg AH, Rajala MW, et al. (2003). Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. Diabetes 52:268–76.

Cristancho AG, Lazar MA. (2011). Forming functional fat: a growing understanding of adipocyte differentiation. Nat Rev Mol Cell Biol 12:722–34.

Davis MA, Ettinger WH, Neuhaus JM, et al. (1989). The association of knee injury and obesity with unilateral and bilateral osteoarthritis of the knee. Am J Epidemiol 130:278–88.

de Boer TN, van Spil WE, Huisman AM, et al. (2012). Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthr Cartil 20:846–53.

Degawa-Yamauchi M. (2003). Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metabol 88:5452–5.

Ding C, Parameswaran V, Cicuttini F, et al. (2008). Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis 67:1256–61.

Dumond H, Presle N, Terlain B, et al. (2003). Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 48:3118–29.

Eisinger K, Bauer S, Schaffler A, et al. (2012). Chemerin induces CCL2 and TLR4 in synovial fibroblasts of patients with rheumatoid arthritis and osteoarthritis. Exp Mol Pathol 92:90–6.

Englund M, Roos EM, Lohmander LS. (2003). Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum 48:2178–87.

Fantuzzi G. (2005). Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115:911–19; quiz 920.

Fasshauer M, Kralisch S, Klier M, et al. (2003). Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. Biochem Biophys Res Commun 301:1045–50.

Felson DT, Anderson JJ, Naimark A, et al. (1988). Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 109:18–24.

Figenschau Y, Knutsen G, Shahazeydi S, et al. (2001). Human articular chondrocytes express functional leptin receptors. Biochem Biophys Res Commun 287:190–7.

Francin PJ, Abot A, Guillaume C, et al. (2014). Association between adiponectin and cartilage degradation in human osteoarthritis. Osteoarthr Cartil 22:519–26.

Frobell RB, Roos EM, Roos HP, et al. (2010). A randomized trial of treatment for acute anterior cruciate ligament tears. New Engl J Med 363:331–42.

Frobell RB, Roos HP, Roos EM, et al. (2013). Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. Br Med J 346:f232.

Fukuhara A, Matsuda M, Nishizawa M, et al. (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 307:426–30.

Gianotti SM, Marshall SW, Hume PA, Bunt L. (2009). Incidence of anterior cruciate ligament injury and other knee ligament injuries: a national population-based study. J Sci Med Sport 12:622–7.

Goralski KB, McCarthy TC, Hanniman EA, et al. (2007). Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 282:28175–88.

Gosset M, Berenbaum F, Salvat C, et al. (2008). Crucial role of visfatin/pre-B cell colony-enhancing factor in matrix degradation and prostaglandin E2 synthesis in chondrocytes: possible influence on osteoarthritis. Arthritis Rheum 58:1399–409.

Griffin TM, Huebner JL, Kraus VB, et al. (2012). Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum 64:443–53.

Griffin TM, Huebner JL, Kraus VB, Guilak F. (2009). Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis. Arthritis Rheum 60:2935–44.

Guermazi A, Hayashi D, Roemer FW, et al. (2014). Synovitis in knee osteoarthritis assessed by contrast-enhanced magnetic resonance imaging (MRI) is associated with radiographic tibiofemoral osteoarthritis and MRI-detected widespread cartilage damage: the MOST study. J Rheumatol 41:501–8.

Ha YJ, Kang EJ, Song JS, et al. (2014). Plasma chemerin levels in rheumatoid arthritis are correlated with disease activity rather than obesity. Joint Bone Spine 81:189–90.

Hamrick MW, Pennington C, Newton D, et al. (2004). Leptin deficiency produces contrasting phenotypes in bones of the limb and spine. Bone 34:376–83.

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

Huang K, Du G, Li L, et al. (2012). Association of chemerin levels in synovial fluid with the severity of knee osteoarthritis. Biomarkers 17:16–20.

Hui W, Litherland GJ, Elias MS, et al. (2012). Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. Ann Rheum Dis 71:455–62.

Jacques C, Holzenberger M, Mladenovic Z, et al. (2012). Proinflammatory actions of visfatin/nicotinamide phosphoribosyl-transferase (Nampt) involve regulation of insulin signaling pathway and Nampt enzymatic activity. J Biol Chem 287:15100–8.

Jiang L, Tian W, Wang Y, et al. (2012). Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 79:291–7.

Karvonen-Gutierrez CA, Harlow SD, Mancuso P, et al. (2013). Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women. Arthritis Care Res (Hoboken) 65: 936–44.

Karvonen-Gutierrez CA, Harlow SD, Jacobson J, et al. (2014). The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. Ann Rheum Dis 73:883–9.

Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. (2012). Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. Osteoarthr Cartil 20:614–21.

Kessler MA, Behrend H, Henz S, et al. (2008). Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. Knee Surg Sports Traumatol Arthrosc 16:442–8.

Koskinen A, Vuolteenaho K, Nieminen R, et al. (2011). 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 29:57–64.

Kumada M, Kihara S, Ouchi N, et al. (2004). Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 109:2046–9.

Laiguillon MC, Houard X, Bougault C, et al. (2014). Expression and function of visfatin (Nampt), an adipokine-enzyme involved in inflammatory pathways of osteoarthritis. Arthritis Res Ther 16:R38.

Lebel B, Hulet C, Galaud B, et al. (2008). Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up. Am J Sports Med 36: 1275–82.

Lee MH, Klein RL, El-Shewy HM, et al. (2008). The adiponectin receptors AdipoR1 and AdipoR2 activate ERK1/2 through a Src/Ras-dependent pathway and stimulate cell growth. Biochemistry 47: 11682–92.

Lee JH, Ort T, Ma K, et al. (2009). Resistin is elevated following traumatic joint injury and causes matrix degradation and release of inflammatory cytokines from articular cartilage *in vitro*. Osteoarthr Cartil/OARS, Osteoarthritis Res Soc 17:613–20.

Li RT, Lorenz S, Xu Y, et al. (2011). Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. Am J Sports Med 39:2595–603.

Licinio J, Negrao AB, Mantzoros C, et al. (1998). Sex differences in circulating human leptin pulse amplitude: clinical implications. J Clin Endocrinol Metab 83:4140–7.

Lira FS, Rosa JC, Pimentel GD, et al. (2012). Both adiponectin and interleukin-10 inhibit LPS-induced activation of the NF-kappaB pathway in 3T3-L1 adipocytes. Cytokine 57:98–106.

Livshits G, Zhai G, Hart DJ, et al. (2009). Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford Study. Arthritis Rheum 60:2037–45.

Lohmander LS, Gerhardsson de Verdier M, Rollof J, et al. (2009). Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 68:490–6.

Lohmander LS, Ostenberg A, Englund M, Roos H. (2004). High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthrit Rheumat 50:3145–52.

Louer CR, Furman BD, Huebner JL, et al. (2012). Diet-induced obesity significantly increases the severity of posttraumatic arthritis in mice. Arthritis Rheum 64:3220–30.

MacDougald OA, Burant CF. (2007). The rapidly expanding family of adipokines. Cell Metab 6:159–61.

Maeda N, Shimomura I, Kishida K, et al. (2002). Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 8:731–7.

Majewski M, Susanne H, Klaus S. (2006). Epidemiology of athletic knee injuries: a 10-year study. Knee 13:184–8.

Mendias CL, Lynch EB, Davis ME, et al. (2013). Changes in circulating biomarkers of muscle atrophy, inflammation, and cartilage turnover in patients undergoing anterior cruciate ligament reconstruction and rehabilitation. Am J Sports Med 41:1819–26.

Miller RE, Tran PB, Das R, et al. (2012). CCR2 chemokine receptor signaling mediates pain in experimental osteoarthritis. Proc Natl Acad Sci USA 109:20602–7.

Moschen AR, Gerner RR, Tilg H. (2010). Pre-B cell colony enhancing factor/NAMPT/visfatin in inflammation and obesity-related disorders. Curr Pharm Des 16:1913–20.

Muruganandan S, Dranse HJ, Rourke JL, et al. (2013). Chemerin neutralization blocks hematopoietic stem cell osteoclastogenesis. Stem Cells 31:2172–82.

Muruganandan S, Roman AA, Sinal CJ. (2010). Role of chemerin/CMKLR1 signaling in adipogenesis and osteoblastogenesis of bone marrow stem cells. J Bone Miner Res 25:222–34.

Muruganandan S, Sinal CJ. (2014). The impact of bone marrow adipocytes on osteoblast and osteoclast differentiation. IUBMB Life.

Neuman P, Englund M, Kostogiannis I, et al. (2008). Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. Am J Sports Med 36:1717–25.

Ohba S, Lanigan TM, Roessler BJ. (2010). Leptin receptor JAK2/STAT3 signaling modulates expression of Frizzled receptors in articular chondrocytes. Osteoarthr Cartil 18:1620–9.

Oliveria SA, Felson DT, Cirillo PA, et al. (1999). Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 10:161–6.

Otero M, Lago R, Gomez R, et al. (2006). Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 65:1198–201.

Perruccio AV, Mahomed NN, Chandran V, Gandhi R. (2014). Plasma adipokine levels and their association with overall burden of painful joints among individuals with hip and knee osteoarthritis. J Rheumatol 41:334–7.

Pessler F, Dai L, Diaz-Torne C, et al. (2008). The synovitis of ''non-inflammatory'' orthopaedic arthropathies: a quantitative histological and immunohistochemical analysis. Ann Rheumat Dis 67:1184–7.

Pirkola J, Vaarasmaki M, Ala-Korpela M, et al. (2010). Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. Am J Epidemiol 171:72–82.

Presle N, Pottie P, Dumond H, et al. (2006). Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthr Cartil 14:690–5.

Proenca AR, Sertie RA, Oliveira AC, et al. (2014). New concepts in white adipose tissue physiology. Braz J Med Biol Res 47:192–205.

Roemer FW, Guermazi A, Felson DT, et al. (2011). Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 70:1804–09.

Roemer FW, Zhang Y, Niu J, et al. (2009). Tibiofemoral joint osteoarthritis: risk factors for MR-depicted fast cartilage loss over a 30-month period in the multicenter osteoarthritis study. Radiology 252:772–80.

Roos EM. (2005). Joint injury causes knee osteoarthritis in young adults. Curr Opin Rheumatol 17:195–200.

Shin HY, Lee DC, Chu SH, et al. (2012). Chemerin levels are positively correlated with abdominal visceral fat accumulation. Clin Endocrinol (Oxf) 77:47–50.

Sokolove J, Lepus CM. (2013). Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis 5:77–94.

Staikos C, Ververidis A, Drosos G, et al. (2013). The association of adipokine levels in plasma and synovial fluid with the severity of knee osteoarthritis. Rheumatology (Oxford) 52:1077–83.

Stannus OP, Cao Y, Antony B, et al. (2013). Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. Ann Rheum Dis 72:535–40.

Steppan CM, Bailey ST, Bhat S, et al. (2001). The hormone resistin links obesity to diabetes. Nature 409:307–12.

Steppan CM, Lazar MA. (2002). Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 13:18–23.

Tong KM, Chen CP, Huang KC, et al. (2011). Adiponectin increases MMP-3 expression in human chondrocytes through AdipoR1 signaling pathway. J Cell Biochem 112:1431–40.

Tsatsanis C, Zacharioudaki V, Androulidaki A, et al. (2005). Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance

to itself and other pro-inflammatory stimuli. Biochem Biophys Res Commun 335:1254–63.

Valcamonica E, Chighizola CB, Comi D, et al. (2014). Levels of chemerin and interleukin 8 in the synovial fluid of patients with inflammatory arthritides and osteoarthritis. Clin Exp Rheumatol 32: 243–50.

Van Spil WE, Welsing PM, Kloppenburg M, et al. (2012). Cross-sectional and predictive associations between plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. Osteoarthr Cartil 20:1278–85.

Visser AW, de Mutsert R, Loef M, et al. (2014). The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. Osteoarthr Cartil 22:197–202.

von Porat A. (2004). High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. Ann Rheumat Dis 63: 269–73.

Weiss E. (2014). Knee osteoarthritis, body mass index and pain: data from the Osteoarthritis Initiative. Rheumatology (Oxford).

Wolf AM, Wolf D, Rumpold H, et al. (2004). Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 323:630–5.

Xue Y, Jiang L, Cheng Q, et al. (2012). Adipokines in psoriatic arthritis patients: the correlations with osteoclast precursors and bone erosions. PLoS One 7:e46740.

Yusuf E, Ioan-Facsinay A, Bijsterbosch J, et al. (2011). Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 70: 1282–4.