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Minireview

Leptin in osteoarthritis: Focus on articular cartilage and chondrocytes

Morena Scotece [a,b,*], Ali Mobasheri [b,c,d]

[a] SERGAS, Research Laboratory 9 (NEIRID LAB: Neuroendocrine Interactions in Rheumatology and Inflammatory Diseases), Institute of Medical Research (IDIS), Santiago University Clinical Hospital, Santiago de Compostela 15706, Spain
[b] The D-BOARD European Consortium for Biomarker Discovery, Department of Veterinary Preclinical Sciences, School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom
[c] Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Arthritis Research UK Pain Centre, Medical Research Council and Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom
[d] Center of Excellence in Genomic Medicine Research (CEGMR), King Fahd Medical Research Center (KFMRC), King AbdulAziz University, Jeddah 21589, Saudi Arabia

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ABSTRACT

Osteoarthritis (OA) is a complex joint disorder with a number of underlying physical, biochemical, biomechanical and genetic causes. Obesity is considered to be one of the major risk factors for the development and progression of OA. It actively contributes to the inflammatory status and to cartilage degradation in the OA joints. Recent data suggests that metabolic factors produced by white adipose tissue, such as leptin, may provide a mechanistic link between obesity and OA, providing an explanation for the high prevalence of OA among obese and over-weight individuals. The unbalanced production of catabolic and anabolic mediators by chondrocytes, the only cell type present in cartilage, determines cartilage degradation, which is the central pathological feature of OA. Evidence is accumulating to support a key role for leptin in the pathogenesis and/or progression of OA. The goal of this focused review is to summarize the current knowledge on the role of leptin in OA with particular emphasis on the effects of this adipokine in cartilage and chondrocyte pathophysiology.

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1. Introduction

Osteoarthritis (OA) is one of the most common disorders of load-bearing synovial joints. Its incidence is steadily increasing worldwide and it is associated with a significant economic burden in the developed and developing countries. A study published in 2006, reported that OA affects more than 37% of US citizens whose age were over 60 years [1]. The destruction and loss of articular cartilage have long been considered to be the central pathological feature of OA. However, this concept has been challenged in recent years and OA is now considered as a global joint disorder that may affect the whole joint (including subchondral bone, muscle, peri-articular ligament and synovium). Advancing age is another strong risk factor for OA development. The age-dependent deterioration of chondrocytes, termed "chondrosenescence", is a consequence of replicative and stress-induced factors, resulting in the development of a "senescent secretory phenotype" [2]. Physicochemical

* Corresponding author.
E-mail addresses: morena.scotece@sergas.es (M. Scotece), anerom84@hotmail.it (A. Mobasheri).

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and biomechanical stimuli also are reported to reduce extracellular osmolarity, resulting in reduced viscoelastic tissue properties contributing to cartilage deformation [3–5]. However, other factors, such as obesity, trauma and physically demanding occupations also increase the risk of OA [6,7].

It has long been recognized that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. Nevertheless, several studies have reported the association between obesity and OA also in non-weight-bearing joints (fingers and wrists) [8]. Moreover, recent results suggest that additional metabolic factors, produced by white adipose tissue (WAT), may also be responsible for the high prevalence of OA among overweight people [9]. Adipocyte-derived molecules, better known as "adipokines", are closely associated with obesity and play an important role in cartilage and bone homeostasis. Thus, adipokines are likely to be important mediators linking obesity and adiposity with inflammation and OA (Fig. 1).

In the present review, we summarize the current knowledge on the first identified adipokine, leptin, focusing our attention on its effects on articular cartilage and chondrocyte function.

1.1. Leptin and leptin receptors

Leptin was the first adipocyte-derived hormone to be described in 1994 by Zhang et al. [10]. Human leptin is a 16-kDa protein encoded by the gene located on chromosome 7q31.3 [11]. Other tissues, such as intestine, placenta, mammary glands, gastric epithelium, skeletal muscle, brain [12], joint tissues and bone [13–18] also produce various quantities of leptin. This hormone acts in the brain as an appetite-regulating factor that induces a decrease in food intake and an increase in energy consumption by inducing anorexigenic factors and suppressing orexigenic neuropeptides [19]. Leptin signals through specific binding to the leptin receptors (OBR). OBRs are encoded by the diabetes (db) gene and belong to the class I cytokine receptor superfamily, which also includes receptors for IL-6, LIF, CNTF, OSM, G-CSF and gp130. Six alternatively spliced isoforms of OB-R have been identified. These isoforms contain identical extracellular binding domains but differ by the length of their cytoplasmic domains: a long isoform (OB-Rb), 4 short isoforms (OB-Ra, OB-Rc, OB-Rd and OB-Rf), and soluble isoform (OB-Re). However, only the long form (OB-Rb), which has the full intracellular domain, with the typical signaling elements of cytokine receptors, is able to transduce the leptin-binding signal to the nucleus. Leptin circulates both as a biologically active free form and a presumably inactive bound form associated with plasma proteins and the soluble leptin receptor isoform OB-Re [20].

The leptin receptor (Ob-Rb) does not have intrinsic tyrosine kinase activity but upon leptin binding, it recruits cytoplasmic kinases like JAK2 to start leptin signaling [21,22]. The ability of leptin receptor to form homodimers facilitates the autophosphorylation of JAK2 [23,24]. Once JAK2 is activated, it is phosphorylated in three tyrosine residues (Tyr985, Tyr1077, Tyr1138) and each tyrosine phosphorylation site is involved with the recruitment of other different signaling proteins [25]. Among these proteins there are STAT members such as STAT3. In addition to the canonical JAK/STAT pathway, leptin receptor signals through other alternative pathways including the ERK1/2, p38, JNK, PKC, SHP2/GRB2 and PI3K/AKT pathways [25–33].

1.2. Leptin and OA

Plasma leptin levels in OA patients correlate positively with BMI. Plasma leptin concentrations are 3 times higher in premenopausal women than men [13,34,35]. The group of Karvonen-Gutierrez showed a positive association between plasma leptin levels and knee OA in middle-aged women [36].

Leptin has been detected also in the synovial fluid (SF) obtained from OA patients and interestingly, leptin levels measured in the joint fluid exceed those found in serum [15]. In addition, Ku et al. reported that SF leptin levels correlate positively with the radiographic severity of OA [37] and also with MMP-1 and MMP-3 levels in OA patients [33], suggesting the possible use of leptin as a potential biomarker for quantitative detection of OA [37]. In a recent study, SF leptin concentrations are associated also with knee and hip pain in OA patients [38].

Griffin and co-workers further investigated the relationships between leptin, obesity and OA in mice. They demonstrated that obesity *per se* is not a sufficient condition for the development of obesity-associated OA [39]. Actually, adiposity in the absence of leptin signaling is insufficient to induce systemic inflammation and knee OA. This is an important point that is often neglected when this issue is discussed in the literature.

In spite of the results obtained in rodent models, correlations that have been observed were between radiographic OA and leptin in patients with hand OA [8,40]. On the contrary, in another study involving 170 patients with knee and hand OA, baseline leptin was associated with increased levels of bone formation biomarkers (osteocalcin and PINP) over 2 years of followup, while OB-Re was associated with

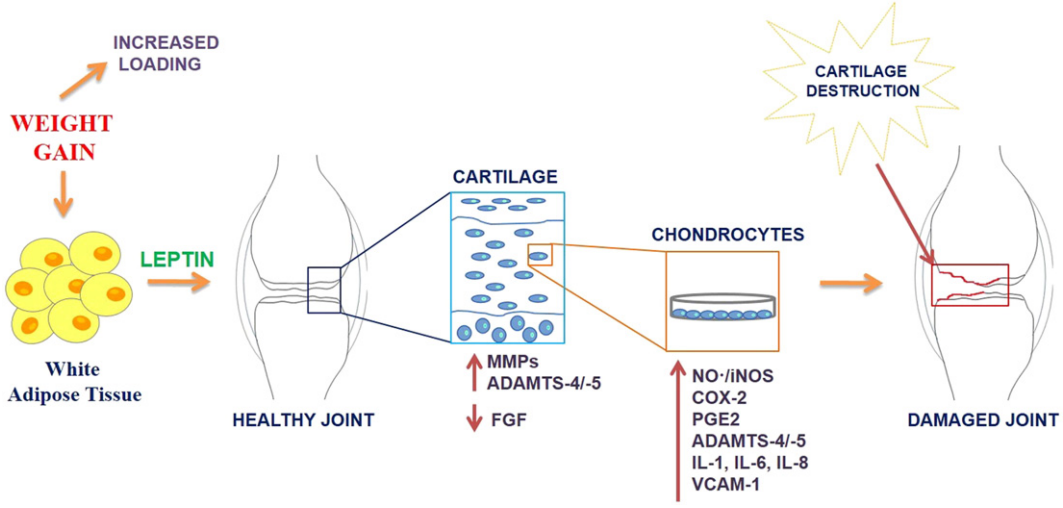

Fig. 1. Schematic representation of the effects of leptin on articular cartilage and chondrocytes.

reduced levels of osteocalcin. In addition, baseline OB-Re was associated with reduced levels of the cartilage formation biomarker PIIANP, an increased cartilage defect score, and increased cartilage volume loss over the same period of time. All results were independent of age, sex, and body mass index. These findings support the concept that serum leptin may provide a non-mechanical link between obesity and joint integrity (which may be mediated by bone and cartilage turnover) that subsequently results in changes to the cartilage defect score and cartilage volume loss [41].

At present, there is no clear consensus regarding the role of leptin in OA. Therefore, further mechanistic studies in larger cohorts of well phenotyped patients are needed to clarify and provide new information about the association between leptin and the development and progression of OA.

1.3. Leptin: influence on cartilage and chondrocyte functions

Several studies have provided clear evidence for a key role of leptin in cartilage homoeostasis. It is known that *in vivo* injection of leptin into the rat knee joint drives catabolic effects in OA cartilage by increasing the production of matrix metalloproteinases (MMPs) such as MMP-1, MMP-3, MMP-9 and MMP-13 [42]. Furthermore, the study of Iliopoulos reported that the treatment of cartilage from OA patients with siRNA targeted for leptin showed decreased MMP-13 expression [17]. Leptin treatment also increased the transcriptional expression of two important aggrecanases, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and -5 in rat articular cartilage. In addition, in the same study a decrease of anabolic factors such as basic fibroblast growth factors (FGF) after leptin treatment was reported [42] (Fig. 1). These results confirmed a catabolic role for leptin in cartilage homeostasis in OA joints.

Leptin and its functional receptor have been identified in the chondrocyte, the only cell type present in the cartilage [43]. OA chondrocytes produce higher leptin concentrations than normal (healthy) chondrocytes. One of the pro-inflammatory mediators that promotes apoptosis, chondrocyte phenotype loss, and MMP activation is nitric oxide (NO). The NEIRID group demonstrated that leptin can directly participate in the damage that occurs in joints by triggering inducible nitric oxide synthase (iNOS) in synergy with interferon γ (IFNγ), *via* a molecular mechanism that involves JAK2 [44]. Our group has also demonstrated that leptin also synergizes with IL-1β, a classic pro-inflammatory cytokine involved in cartilage damage [45] enhancing the production of iNOS, prostaglandin E_2 (PGE_2) and cyclooxygenase-2 (COX-2) in human chondrocytes [29,45]. Very recently, the group of Yaykasli demonstrated that leptin treatment in human chondrocytes increases ADAMTS^{-4}, ADAMTS^{-5}, and ADAMTS^{-9} gene expression by mitogen-activated protein kinases and NF-κB signaling pathways [46].

Several studies reported the ability of leptin to secrete higher levels of pro-inflammatory cytokines implicated in cartilage degradation such as Interleukin-1 β (IL-1β), IL-6 and IL-8 [29,47] by articular chondrocytes. Very recently, Conde et al. showed increased expression of vascular cell adhesion molecule (VCAM-1) after leptin treatment in human and murine chondrocytes [48] (Fig. 1).

In contrast, studies have also reported anabolic activities of leptin in cartilage metabolism. The group of Figenschau demonstrated increased proliferation of chondrocytes and enhanced synthesis of proteoglycans and collagen after leptin incubation. Recent studies have provided evidence that treatment of chondrocytes with leptin can promote proliferation, differentiation, type X collagen production and cytoskeletal remodeling *via* a RhoA/RhoA kinase (ROCK) pathway [49–51]. In addition, Kishida et al. showed a reduction of type X collagen in growth plates from ob/ob mice [52]. These results showing anabolic activities of leptin in cartilage metabolism suggesting that the catabolic effects of leptin may trigger compensatory anabolic responses, which is typical of the early OA process [43]. Therefore, it is clear that leptin is capable of exerting both pro-inflammatory and anabolic effects.

2. Conclusions

Although it is evident that biomechanical forces contribute to joint destruction in obese patients, circulating factors, such as leptin, may also contribute to the pathogenesis and/or progression of OA. The evidence summarized in this concise review suggests that leptin is involved in the pathophysiology of OA at local and systemic levels. As reported above, leptin increases catabolic factors in cartilage and chondrocytes, suggesting a possible role as a future drug target for therapy in bone and joint diseases. The use of specific molecules with a high affinity for binding circulating leptin, might be a potential approach. In addition, another way to control leptin activity, might involve blocking the leptin receptor with monoclonal humanized antibodies or mutant leptin analogs that are able to bind the receptor without activating it. Obviously, the receptors that mediate the central effect of leptin on food intake, should not be blocked, since the consequences would be hyperphagia and obesity and this approach could potentially have many other systemic effects. Moreover, leptin levels are associated with OA progression, suggesting a possible role of this adipokine as a good biomarker for monitoring disease progression. Further molecular, preclinical and clinical studies are needed to understand the role of leptin in bone and cartilage diseases and clarify the potential role of this adipokine as a biomarker and one of the mechanistic links between diet, obesity, adiposity and OA.

Abbreviations

OA	osteoarthritis
WAT	white adipose tissue
SF	synovial fluid
MMPs	matrix metalloproteinases
NO	nitric oxide
FGF	fibroblast growth factor
iNOS	inducible nitric oxide synthase
IFN-γ	interferon-γ
PGE_2	prostaglandin E_2
COX-2	cyclooxygenase-2

Conflict of interest statement

The authors wrote this paper within the scope of their academic and affiliated research positions. The authors declare no conflicts of interest. The authors do not have any commercial relationships that could be construed as biased or inappropriate.

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References

[1] C.F. Dillon, E.K. Rasch, Q. Gu, R. Hirsch, Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991–94, J. Rheumatol. 33 (11) (2006) 2271–2279.

[2] A. Mobasheri, C. Matta, R. Zakany, G. Musumeci, Chondrosenescence: definition, hallmarks and potential role in the pathogenesis of osteoarthritis, Maturitas 80 (3) (2015) 237–244.
[3] A.I. Maroudas, Balance between swelling pressure and collagen tension in normal and degenerate cartilage, Nature 260 (5554) (1976) 808–809.
[4] R.A. Bank, M. Soudry, A. Maroudas, J. Mizrahi, J.M. TeKoppele, The increased swelling and instantaneous deformation of osteoarthritic cartilage is highly correlated with collagen degradation, Arthritis Rheum. 43 (2210) (2000) 2202–2210.
[5] H. Jahr, C. Matta, A. Mobasheri, Physicochemical and biomechanical in cell-based articular cartilage repair, Curr. Rheumatol. Rep. (2015), http://dx.doi.org/10.1007/S11926-014-0493-9.
[6] A.D. Woolf, B. Pfleger, Burden of major musculoskeletal conditions, Bull. World Health Organ. 81 (9) (2003) 646–656.
[7] L.S. Lohmander, E.M. Roos, Clinical update: treating osteoarthritis, Lancet 370 (9605) (2007) 2082–2084.
[8] E. Yusuf, R.G. Nelissen, A. Ioan-Facsinay, V. Stojanovic-Susulic, J. DeGroot, G. van Osch, S. Middeldorp, T.W. Huizinga, M. Kloppenburg, Association between weight or body mass index and hand osteoarthritis: a systematic review, Ann. Rheum. Dis. 69 (4) (2010) 761–765.
[9] P. Pottie, N. Presle, B. Terlain, P. Netter, D. Mainard, F. Berenbaum, Obesity and osteoarthritis: more complex than predicted! Ann. Rheum. Dis. 65 (11) (2006) 1403–1405.
[10] Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, J.M. Friedman, Positional cloning of the mouse obese gene and its human homologue, Nature 372 (6505) (1994) 425–432.
[11] Green ED, Maffei M, Braden VV, Proenca R, DeSilva U, Zhang Y, Chua SC, Jr., Leibel RL, Weissenbach J, Friedman JM. The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome 7. Genome Res. 1995;5 (1):5–12.
[12] R.S. Ahima, J.S. Flier, Adipose tissue as an endocrine organ, Trends Endocrinol. Metab. 11 (8) (2000) 327–332.
[13] H. Dumond, N. Presle, B. Terlain, D. Mainard, D. Loeuille, P. Netter, P. Pottie, Evidence for a key role of leptin in osteoarthritis, Arthritis Rheum. 48 (11) (2003) 3118–3129.
[14] M. Morroni, R. De Matteis, C. Palumbo, M. Ferretti, I. Villa, A. Rubinacci, S. Cinti, G. Marotti, In vivo leptin expression in cartilage and bone cells of growing rats and adult humans, J. Anat. 205 (4) (2004) 291–296.
[15] N. Presle, P. Pottie, H. Dumond, C. Guillaume, F. Lapicque, S. Pallu, D. Mainard, P. Netter, B. Terlain, Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of Joint Tissues to Their Articular Production, Osteoarthr. Cartil. 14 (7) (2006) 690–695.
[16] T. Simopoulou, K.N. Malizos, D. Iliopoulos, N. Stefanou, L. Papatheodorou, M. Ioannou, A. Tsezou, Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism, Osteoarthr. Cartil. 15 (8) (2007) 872–883.
[17] D. Iliopoulos, K.N. Malizos, A. Tsezou, Epigenetic regulation of leptin affects MMP-13 expression in osteoarthritic chondrocytes: possible molecular target for osteoarthritis therapeutic intervention, Ann. Rheum. Dis. 66 (12) (2007) 1616–1621.
[18] K. Jarvinen, K. Vuolteenaho, R. Nieminen, T. Moilanen, R.G. Knowles, E. Moilanen, Selective iNOS inhibitor 1400 W enhances anti-catabolic IL-10 and reduces destructive MMP-10 in OA cartilage. Survey of the effects of 1400 W on inflammatory mediators produced by OA cartilage as detected by protein antibody array, Clin. Exp. Rheumatol. 26 (2) (2008) 275–282.
[19] M.A. Cowley, J.L. Smart, M. Rubinstein, M.G. Cerdan, S. Diano, T.L. Horvath, R.D. Cone, M.J. Low, Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus, Nature 411 (6836) (2001) 480–484.
[20] M.K. Sinha, J. Sturis, J. Ohannesian, S. Magosin, T. Stephens, M.L. Heiman, K.S. Polonsky, J.F. Caro, Ultradian oscillations of leptin secretion in humans, Biochem. Biophys. Res. Commun. 228 (3) (1996) 733–738.
[21] N. Ghilardi, R.C. Skoda, The leptin receptor activates janus kinase 2 and signals for proliferation in a factor-dependent cell line, Mol. Endocrinol. 11 (4) (1997) 393–399.
[22] G. Bahrenberg, I. Behrmann, A. Barthel, P. Hekerman, P.C. Heinrich, H.G. Joost, W. Becker, Identification of the critical sequence elements in the cytoplasmic domain of leptin receptor isoforms required for Janus kinase/signal transducer and activator of transcription activation by receptor heterodimers, Mol. Endocrinol. 16 (4) (2002) 859–872.
[23] D.W. White, K.K. Kuropatwinski, R. Devos, H. Baumann, L.A. Tartaglia, Leptin receptor (OB-R) signaling. Cytoplasmic domain mutational analysis and evidence for receptor homo-oligomerization, J. Biol. Chem. 272 (7) (1997) 4065–4071.
[24] R. Devos, Y. Guisez, J. Van der Heyden, D.W. White, M. Kalai, M. Fountoulakis, G. Plaetinck, Ligand-independent dimerization of the extracellular domain of the leptin receptor and determination of the stoichiometry of leptin binding, J. Biol. Chem. 272 (29) (1997) 18304–18310.
[25] A.S. Banks, S.M. Davis, S.H. Bates, M.G. Myers Jr., Activation of downstream signals by the long form of the leptin receptor, J. Biol. Chem. 275 (19) (2000) 14563–14572.
[26] C. Bjorbaek, S. Uotani, B. da Silva, J.S. Flier, Divergent signaling capacities of the long and short isoforms of the leptin receptor, J. Biol. Chem. 272 (51) (1997) 32686–32695.
[27] O. Gualillo, S. Eiras, D.W. White, C. Dieguez, F.F. Casanueva, Leptin promotes the tyrosine phosphorylation of SHC proteins and SHC association with GRB2, Mol. Cell. Endocrinol. 190 (1–2) (2002) 83–89.
[28] K.D. Niswender, G.J. Morton, W.H. Stearns, C.J. Rhodes, M.G. Myers Jr., M.W. Schwartz, Intracellular signalling. Key enzyme in leptin-induced anorexia, Nature 413 (6858) (2001) 794–795.
[29] K. Vuolteenaho, A. Koskinen, M. Kukkonen, R. Nieminen, U. Paivarinta, T. Moilanen, E. Moilanen, Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage-mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production, Mediat. Inflamm. 2009 (2009) 345838.
[30] Y. Akasaka, M. Tsunoda, T. Ogata, T. Ide, K. Murakami, Direct evidence for leptin-induced lipid oxidation independent of long-form leptin receptor, Biochim. Biophys. Acta 1801 (10) (2010) 1115–1122.
[31] B.F. Belgardt, A. Husch, E. Rother, M.B. Ernst, F.T. Wunderlich, B. Hampel, T. Klockener, D. Alessi, P. Kloppenburg, J.C. Bruning, PDK1 deficiency in POMC-expressing cells reveals FOXO1-dependent and -independent pathways in control of energy homeostasis and stress response, Cell Metab. 7 (4) (2008) 291–301.
[32] A. Oswal, G. Yeo, Leptin and the control of body weight: a review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity, Obesity (Silver Spring) 18 (2) (2010) 221–229.
[33] A. Koskinen, K. Vuolteenaho, R. Nieminen, T. Moilanen, E. Moilanen, 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 (1) (2011) 57–64.
[34] O. Gualillo, S. Eiras, F. Lago, C. Dieguez, F.F. Casanueva, Elevated serum leptin concentrations induced by experimental acute inflammation, Life Sci. 67 (20) (2000) 2433–2441.
[35] M. Rosenbaum, M. Nicolson, J. Hirsch, S.B. Heymsfield, D. Gallagher, F. Chu, R.L. Leibel, Effects of gender, body composition, and menopause on plasma concentrations of leptin, J. Clin. Endocrinol. Metab. 81 (9) (1996) 3424–3427.
[36] C.A. Karvonen-Gutierrez, S.D. Harlow, P. Mancuso, J. Jacobson, C.F. Mendes de Leon, B. Nan, Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women, Arthritis Care Res. 65 (6) (2013) 936–944 (Hoboken).
[37] J.H. Ku, C.K. Lee, B.S. Joo, B.M. An, S.H. Choi, T.H. Wang, H.L. Cho, Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis, Clin. Rheumatol. 28 (12) (2009) 1431–1435.
[38] A. Lubbeke, A. Finckh, G.J. Puskas, D. Suva, A. Ladermann, S. Bas, D. Fritschy, C. Gabay, P. Hoffmeyer, Do synovial leptin levels correlate with pain in end stage arthritis? Int. Orthop. 37 (10) (2013) 2071–2079.
[39] T.M. Griffin, J.L. Huebner, V.B. Kraus, F. Guilak, Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis, Arthritis Rheum. 60 (10) (2009) 2935–2944.
[40] M. Massengale, B. Lu, J.J. Pan, J.N. Katz, D.H. Solomon, Adipokine hormones and hand osteoarthritis: radiographic severity and pain, PLoS One 7 (10) (2012) e47860.
[41] P.A. Berry, S.W. Jones, F.M. Cicuttini, A.E. Wluka, R.A. Maciewicz, 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 (3) (2011) 700–707.
[42] J.P. Bao, W.P. Chen, J. Feng, P.F. Hu, Z.L. Shi, L.D. Wu, Leptin plays a catabolic role on articular cartilage, Mol. Biol. Rep. 37 (7) (2010) 3265–3272.
[43] Y. Figenschau, G. Knutsen, S. Shahazeydi, O. Johansen, B. Sveinbjornsson, Human articular chondrocytes express functional leptin receptors, Biochem. Biophys. Res. Commun. 287 (1) (2001) 190–197.
[44] M. Otero, J.J. Gomez Reino, O. Gualillo, Synergistic induction of nitric oxide synthase type II: in vitro effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells, Arthritis Rheum. 48 (2) (2003) 404–409.
[45] M. Otero, R. Lago, F. Lago, J.J. Reino, O. Gualillo, Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1, Arthritis Res. Ther. 7 (3) (2005) R581–R591.
[46] K.O. Yaykasli, O.F. Hatipoglu, E. Yaykasli, K. Yildirim, E. Kaya, M. Ozsahin, M. Uslu, E. Gunduz, Leptin induces ADAMTS^{-4}, ADAMTS^{-5}, and ADAMTS^{-9} genes expression by mitogen-activated protein kinases and NF-kB signaling pathways in human chondrocytes, Cell Biol. Int. 39 (1) (2015) 104–112.
[47] R. Gomez, M. Scotece, J. Conde, J.J. Gomez-Reino, F. Lago, O. Gualillo, Adiponectin and leptin increase IL-8 production in human chondrocytes, Ann. Rheum. Dis. 70 (11) (2011) 2052–2054.
[48] J. Conde, M. Scotece, V. Lopez, R. Gomez, F. Lago, J. Pino, J.J. Gomez-Reino, O. Gualillo, Adiponectin and leptin induce VCAM-1 expression in human and murine chondrocytes, PLoS One 7 (12) (2012) e52533.
[49] S.J. Wang, X.F. Li, L.S. Jiang, L.Y. Dai, Leptin regulates estrogen receptor gene expression in ATDC5 cells through the extracellular signal regulated kinase signaling pathway, J. Cell. Biochem. 113 (4) (2012) 1323–1332.
[50] J. Liang, J. Feng, W.K. Wu, J. Xiao, Z. Wu, D. Han, Y. Zhu, G. Qiu, Leptin-mediated cytoskeletal remodeling in chondrocytes occurs via the RhoA/ROCK pathway, J. Orthop. Res. 29 (3) (2011) 369–374.
[51] M. Ben-Eliezer, M. Phillip, G. Gat-Yablonski, Leptin regulates chondrogenic differentiation in ATDC5 cell-line through JAK/STAT and MAPK pathways, Endocrine 32 (2) (2007) 235–244.
[52] Y. Kishida, M. Hirao, N. Tamai, A. Nampei, T. Fujimoto, T. Nakase, N. Shimizu, H. Yoshikawa, A. Myoui, Leptin regulates chondrocyte differentiation and matrix maturation during endochondral ossification, Bone 37 (5) (2005) 607–621.