Relation between Adipokines and Radiological Changes in Patients with Knee Osteoarthritis

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Abstract: Background: Osteoarthritis (OA) is the most common degenerative articular disease caused by joint degeneration, weight-bearing joints, and the knee is most frequently involved. Since the mechanical factors can't explain incidence of osteoarthritis (OA), attention had been shifted to an obesity-related systemic factor as a link between obesity and OA. Adipokines (ADK) were proposed as a predictor markers and potential systemic factor, which links obesity to OA. **Objective:** to investigate the association of ADK with OA and their potential to be used as biomarkers for OA activity and its relation with radiological grading. **Subjects and Methods:** Serum levels of adipokines (adiponectin (ADP), leptin (LEP), visfatin and resistin) were determined in 40 patients with primary knee OA who had evidence of radiological changes in the knee by plain x-ray. **Results:** serum ADP, LEP, visfatin and resistin were significantly higher in the patients KOA compared to the controls (P=0.008, 0.002, <0.001, and <0.001, respectively) BMI is significantly correlated with serum ADP, LEP, visfatin and resistin. In addition, serum levels of the ADP, LEP, resistin and visfatin were significantly correlated with clinical and radiological markers indicating the severity of the KOA as well as with OA activity. **Conclusion:** Serum ADP, LEP, visfatin and resistin can be used as a marker for KOA activity and severity. These findings strongly suggest that ADK is involved in the pathogenesis of joint inflammation and cartilage damage in OA and may form the link between obesity and development of OA and therefore, may be a target for disease-modifying drug development.
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1. Introduction

Osteoarthritis (OA) is the most common degenerative articular disease and is a major cause of pain and disability in adult population. OA is considered a disease of the whole joint, which is characterized by articular cartilage degradation, subchondral bone sclerosis, osteophyte formation, synovial inflammation, ligaments degeneration, as well as bone and muscle alterations[1]. Idiopathic OA is the most common form of arthritis and is a debilitating progressive disease that affects 60% of men and 70% of women over the age of 65[2, 3]. OA pathogenesis is complex since several factors including genetic, systemic, and local factors interact and initiate a process of cartilage deterioration, with a proliferative reaction of subchondral bone and synovial inflammation [4].

Obesity has been recognized as an important risk factor for the incidence and the progression of knee OA[5, 6]. With obesity set to rise in future years, combined with OA being a frequent condition among the elderly and an ageing population, the prevalence of OA is expected to increase[7]. Obesity was found to contribute to joint tissues degeneration by producing and releasing a plethora of factors called adipokines (ADK)[8]. Adipokines are necessary for cell differentiation and hematopoiesis, among other functions. However, such functions depend on their concentration in the bloodstream. The increase of adipokines beyond the optimal concentration has been found to be already capable of beginning the low-grade inflammatory process[9, 10], and could affect joint tissues homeostasis [8].

ADK are currently considered as key players of the complex network of soluble mediators involved in the pathophysiology of OA[11, 12]. Joint cell populations such as chondrocytes and/or synovial fibroblasts may also produce ADK[13, 14]. This is may explain the association between excess fat mass and the development of OA in non-weight bearing joints in the obese patients[15, 16]. Adipokines are produced in knee OA joints by infrapatellar fat pads, synovium,

chondrocytes, osteoblasts, as well as osteoclasts [13, 17]. It was proposed that plasma and synovial fluid adipokine levels would be related with cartilage degeneration and synovial inflammation[18].

Adiponectin

ADP is very abundant in plasma and circulates in high concentrations at about 5–30 μg/mL accounting for 0.01% of all plasma proteins[19]. Its expression are decreased in obese patients[20,21]. Plasma ADP concentrations were found to be significantly higher in OA patients in comparison to healthy controls[22]. Serum ADP levels and ADP production from OA cartilage are higher in patients who had the radiologically most severe OA[23]. In addition, serum ADP concentration is significantly associated with OA biomarkers and local synovial inflammation[18,23].

Some clinical data also support the fact that ADP could be a protective molecule against development of OA. An inverse correlation between ADP and disease severity was reported[24]. Moreover, it was reported that OA patients with high ADP concentrations had a reduced risk for hand OA progression, indicating that ADP can be a protective molecule against cartilage damage[25]. So, adiponectin has controversial role in OA since it has been exert both protective and adverse effects in joints.

Leptin

LEP is mainly produced by adipocytes, its levels correlated with WAT mass and its synthesis regulated by inflammatory mediators[26]. Serum and synovial fluid LEP concentrations are elevated in obese individuals[13, 27]. Synovial fluid LEP levels was significantly correlated with the radiological severity of OA, proposing that LEP can be a useful marker for OA[28]. LEP is a pro-inflammatory factor and exert a catabolic effect on OA joints. Higher plasma leptin concentration was associated with higher odds ratio of having knee OA, after age, ethnicity and BMI adjustments[29].

Visfatin

Visfatin, also known as pre-B cell colony-enhancing factor, is a highly conserved, 52-kDa protein, consists of 491 amino acids in human[30, 31]. Visceral adipose tissue is regarded to be more important source of visfatin than subcutaneous adipose tissue[32]. Levels of visfatin in plasma and synovial fluid are associated with inflammation and clinical disease activity. Plasma visfatin levels are correlated with C-reactive protein indicating that it may be related to the inflammatory process[12,33]. Visfatin level in synovial fluid is increased in OA patients with more radiographic damage compared with patients with less severe damage. Synovial visfatin levels in grade 4 KL-scores were significantly higher than those of grade 3 KL-scores[34].

Resistin

Resistin is a cysteine-rich adipose-derived peptide hormone that in humans is encoded by the RETN gene[35]. Its expression was greater in WAT than in brown adipose tissue[36]. Plasma resistin concentrations were positively associated with the prevalence of radiographic KOA. The association between resistin and the presence of radiographic KOA was more obvious in OA patients with higher ADP levels[37]. In addition, a positive correlation has been found between synovial resistin levels and systemic markers of inflammation[38]. Moreover, resistin can stimulate inflammatory cytokines, such as IL-6 and TNF-α, as well as prostaglandin E2 synthesis.

In general, radiographic examination is used to confirm the diagnosis of OA. However, the onset of OA is before radiological diagnosis which seen after considerable cartilage loss has already occurred. Therefore, early diagnosis of OA may allow preventive treatments without the destruction of joints[39]. Biomarkers offer a potential alternative mean for earlier diagnosis of OA even in non-symptomatic stages. Therefore, the present study aims to clarify the association of ADK with KOA and their potential to be used as biomarkers for OA activity. In addition, assessed its relation with radiological grading and other variables.

2. Subjects and methods:

Participants

A consecutive 40 patients with symptomatic primary KOA were participate in this study. All patients met the European League Against Rheumatism (EULAR) 2010 diagnosticcriteria for OA of the knee joint[40]. The study also included 40 apparently healthy subjects as a control group.

Clinical assessment

BMI and parameters of KOA activity and functional disabilitywereassessed. In addition, the evidence of radiological changes in patients knees were detected by plain x-ray. Whereas, xclusion Criteria were: a)- Inflammatory arthritis b)- Patients with history of knee trauma, fractures or previous knee surgery c)- Patients with systemic glucocorticoid intake in the last 6 months, or intra-articular glucocorticoid or HA injection in the last 3 or 6 month.

Biochemical assays

After 12 hours fasting, five milliliters venous blood samples were withdrawn from the antecubital vein from all subjects (patients and control). Blood samples were collected on the same day of history taking and clinical examination. Samples were immediately centrifuged at 4^{o}C for mass measurements of serum concentrations of ADP

(Quantikine ELISA Human Total ADP/Acrp30), LEP (DRG International, Inc., USA), resistin (Ray Biotech, Norcross, GA, USA), andvisfatin (Ray Biotech, Norcross, GA, USA) using ELISA assay.

Statistical Analysis

All statistical analyses were performed using SPSS for windows version 20.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ±SD, while categorical data were expressed in number and percentage. The differences between two groups or more were determined using independent samples Student's t test or ANOVA test respectively for variables with continuous data or chi-square test for variables containing categorical data. The correlation between two variables determine by Pearson correlation test. Statistical significance was set at $p<0.05$.

3. Results

Demographic and biochemical characteristics of patients:

The current study consisted of 40 KOA patients (29 females and 11 males) and 40 healthy volunteers as control group. Table1 deals with characteristics of this population, the average age of the patients and control was 54.8 ±6.7 years and 55.3 ±6.6 years respectively. Whereas, the average BMI in the OA patients was 27.3 ±2.8 kg/m^2 and the average BMI in the controls was 25.1 ±2.2 kg/m^2. For all patients included in the study, the average level of serm adiponectin, leptin, visfatin, and resistin were significantly higher in the serum of the KOA patients group in comparison to the controls group (P=0.008, 0.002, and $p<0.001$ for the last two variables respectively), Fig1.

Effect of age, BMI, the parameters of KOA activity and functional disability and other variables on adipokines.

The present study reveals that the BMI is significantly correlated with serum ADP, LEP, visfatin, and with resistin (P =0.008, 0.024, 0.010, and 0.013 respectively). Whereas, the age of the patients did not show a correlation with adipokines, table 2. When the analysis was restricted to gender, the female patients showed significantly higher serum level of ADP, and LEP than in the males (P = 0.016 and 0.011). Whereas, serum level of the resistin in male KOA patients was significantly higher than in the female, P =0.021), and the serum level of visfatin did not differ significantly between the female and male KOA patients, P = 0.062. On the contrary, no correlation was found between duration of KOA and serum adipokines levels, table3.

Regards the parameters of KOA activity and functional disability our results estimated that the serum ADP level was significantly correlated with knee tenderness (P =0.003), VAS pain (P =0.006), activity score (P =0.013) and Womac score (P =0.007), Fig.2. Morever, the serum LEP level was significantly correlated with knee tenderness (P =0.003), VAS pain (P=0.005), activity score (P=0.012) and Womac score (P=0.006) (table4, Fig.3).

On the other hand, serum visfatin and resistin levels were significantly correlated with activity score (P=0.032 and P=0.019, respectively) and with Womac score (P=0.018 and P=0.011) but did not show significant correlation with the tenderness score nor VAS-pain, Fig4,5. In addition, there were significant correlations had been found between the serum adipokines (ADP, LEP, visfatin, and resistin) with KL-grade of x-ray and with the US osteophyte grade. The correlation or association between all variables and adipokines were summarized in table 4.

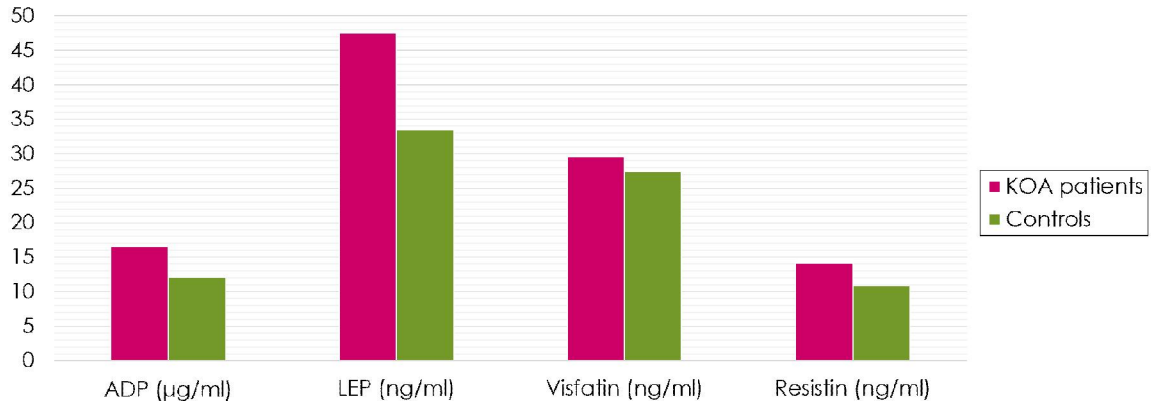

Fig.1. Serum ADP, LEP, visfatin, and resistin levels in the KOA patients and the controls

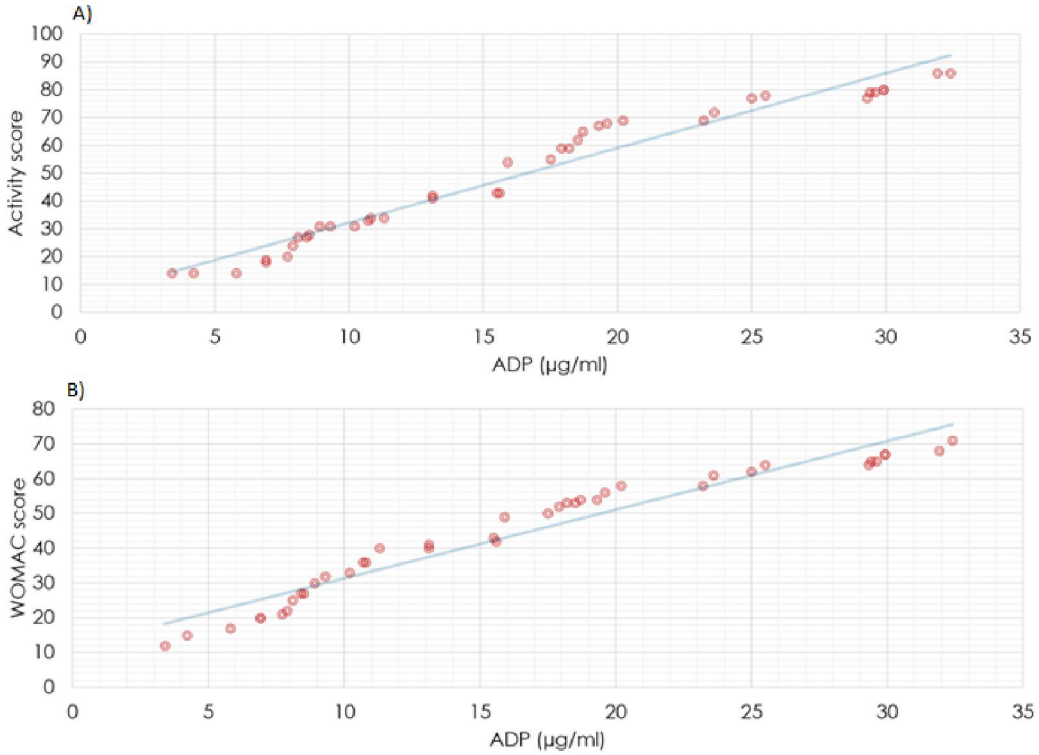

Fig.2. Correlation of serum ADP with A)-Activity score. B)- Womac score in KOA patients

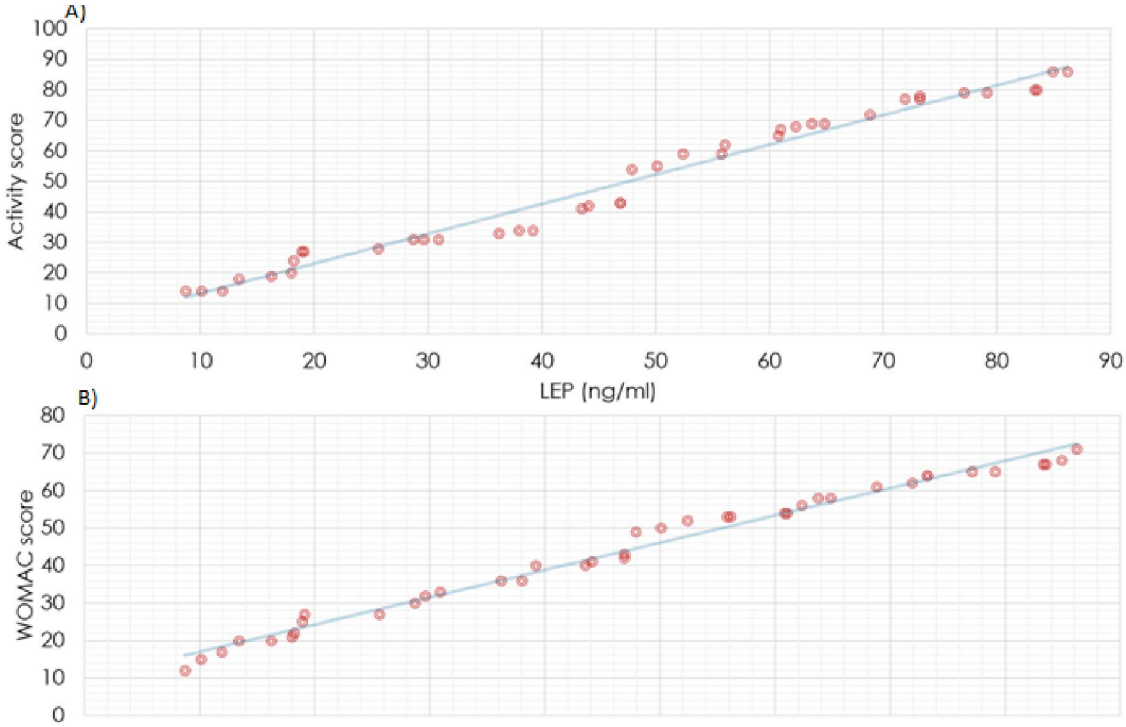

Fig.3. Correlation of serum LEP with A)-Activity score. B)- Womac score in KOA patients

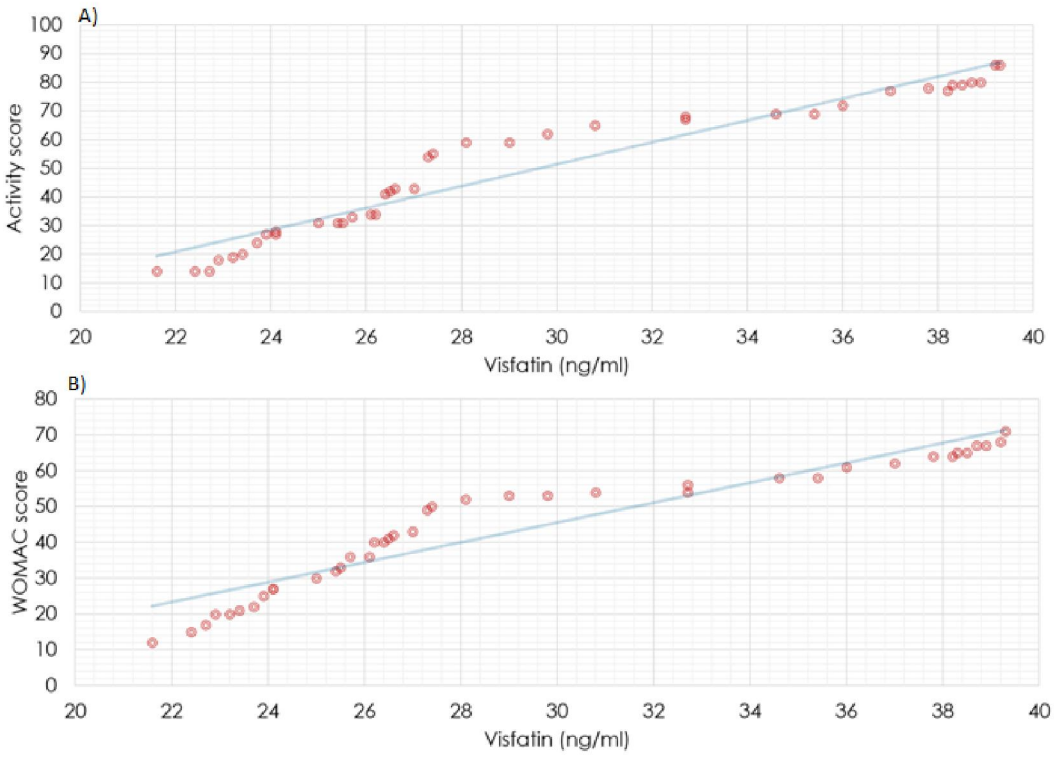

Fig.4. Correlation of serum Visfatin with A)-Activity score. B)- Womac score in KOA patients

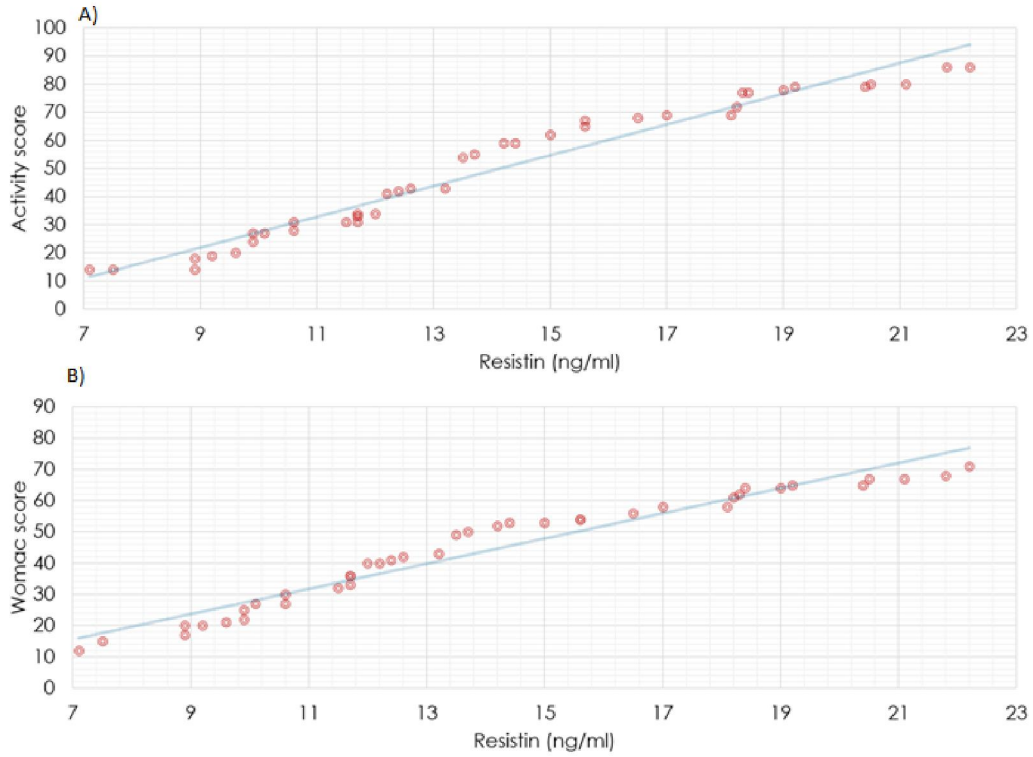

Fig.5. Correlation of serum Resistin with A)-Activity score. B)- Womac score in KOA patients

Table 1. Demographic and biochemical characteristics of the OA patients and controls				
	KOA patients	Controls	Student's t test	
	Mean ±SD	Mean ±SD	T	P
Age (years)	54.8 ±6.7	55.3 ±6.5	0.356	0.723
Sex (n, %)				
Females	29, 72.5%	25, 62.5%	0.912*	0.340
Males	11, 27.5%	15, 37.5%		
BMI (kg/m^2)	27.3 ±2.8	25.1 ±2.2	0.402	0.689
ADP (µg/ml)	16.5 ±8.6	12.1 ±5.7	2.715	0.008
LEP (ng/ml)	47.5 ±23.9	33.5 ±14.4	3.158	0.002
Visfatin (ng/ml)	29.6 ±5.9	27.4 ±3.6	4.377	<0.001
Resistin (ng/ml)	14.1 ±4.2	10.8 ±2.9	4.111	<0.001
*** X^2, Chi square test**				

Table 2. Correlation of serum adipokines levels with age and BMI				
	Age		BMI	
	R	p	r	P
ADP	0.023	0.840	0.416	0.008
LEP	0.033	0.771	0.356	0.024
Visfatin	0.051	0.655	0.402	0.010
Resistin	0.102	0.366	0.389	0.013

Table 3. Correlation of adipokines with knee osteoarthritis

Adipokines	BMI	Serum levels between genders	Age	Duration of KOA	Tenderness	VAS-pain	Activity score	Womac score	KL-grade of x-ray	US osteophyte grade
ADP (µg/ml)	Positive	female > male	Unclear	Unclear	Positive	Positive	Positive	Positive	Positive	Positive
LEP (ng/ml)	Positive	female > male	Unclear	Unclear	Positive	Positive	Positive	Positive	Positive	Positive
Visfatin (ng/ml)	Positive	Unclear	Unclear	Unclear	Unclear	Unclear	Positive	Positive	Positive	Positive
Resistin (ng/ml)	Positive	male > female	Unclear	Unclear	Unclear	Unclear	Positive	Positive	Positive	Positive

Table 4. Correlation of ADP, LEP, visfatin and resistin serum levels with the parameters of KOA activity and functional disability												
	Tenderness		VAS-pain		Activity score		Womac score		KL- grade of x-ray		US osteophyte grade	
	r	P	r	P	r	P	R	P	r	p	r	P
ADP	0.461	0.003	0.426	0.006	0.390	0.013	0.422	0.007	0.348	0.028	0.334	0.035
LEP	0.455	0.003	0.439	0.005	0.395	0.012	0.425	0.006	0.339	0.032	0.335	0.034
Visfatin	0.114	0.485	0.265	0.098	0.339	0.032	0.373	0.018	0.366	0.020	0.349	0.027
Resistin	0.304	0.056	0.267	0.096	0.369	0.019	0.399	0.011	0.347	0.028	0.322	0.043

References

1. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64: 1697-1707.
2. Buckwalter JA, Martin J, Mankin HJ. Synovial joint degeneration and the syndrome of osteoarthritis. Instr Course Lect. 2000;49: 481-489.
3. Sarzi-Puttini P, Cimmino MA, Scarpa R, et al. Osteoarthritis: an overview of the disease and its treatment strategies. Semin Arthritis Rheum. 2005;35: 1-10.
4. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheum Dis Clin North Am. 2004;30: 783-797, vii.
5. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol. 2010;22: 533-537.
6. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138: 185-193.
7. Mabey T, Honsawek S. Cytokines as biochemical markers for knee osteoarthritis. World J Orthop. 2015;6: 95-105.
8. Conde J, Scotece M, Lopez V, et al. Adipokines: novel players in rheumatic diseases. Discov Med. 2013;15: 73-83.

9. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;9: 191-200.
10. Mancuso P. The role of adipokines in chronic inflammation. Immunotargets Ther. 2016;5: 47-56.
11. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6: 772-783.
12. Lago F, Dieguez C, Gomez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol. 2007;3: 716-724.
13. Presle N, Pottie P, Dumond H, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis Cartilage. 2006;14:690-695.
14. Conde J, Scotece M, Lopez V, et al. Adiponectin and leptin induce VCAM-1 expression in human and murine chondrocytes. PLoS One. 2012;7: e52533.
15. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. Obes Rev. 2014;15: 578-586.
16. Isla Pera P, Ferrer MC, Nunez Juarez M, et al. Obesity, knee osteoarthritis, and polypathology: factors favoring weight loss in older people. Patient Prefer Adherence. 2016;10: 957-965.
17. Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? Joint Bone Spine. 2008;75: 669-671.
18. de Boer TN, van Spil WE, Huisman AM, et al. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage. 2012;20: 846-853.
19. Nigro E, Scudiero O, Monaco ML, et al. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int. 2014;2014: 658913.
20. Daniele A, Cammarata R, Masullo M, et al. Analysis of adiponectin gene and comparison of its expression in two different pig breeds. Obesity (Silver Spring). 2008;16: 1869-1874.
21. De Rosa A, Monaco ML, Capasso M, et al. Adiponectin oligomers as potential indicators of adipose tissue improvement in obese subjects. Eur J Endocrinol. 2013;169: 37-43.
22. Laurberg TB, Frystyk J, Ellingsen T, 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: 1885-1891.
23. Koskinen A, Juslin S, Nieminen R, Moilanen T, Vuolteenaho K, Moilanen E. Adiponectin associates with markers of cartilage degradation in osteoarthritis and induces production of proinflammatory and catabolic factors through mitogen-activated protein kinase pathways. Arthritis Res Ther. 2011;13: R184.
24. Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res. 2010;41: 593-598.
25. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis. 2011;70: 1282-1284.
26. Gualillo O, Eiras S, Lago F, Dieguez C, Casanueva FF. Elevated serum leptin concentrations induced by experimental acute inflammation. Life Sci. 2000;67: 2433-2441.
27. Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. FASEB J. 2001;15: 2565-2571.
28. Ku JH, Lee CK, Joo BS, et al. Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. Clin Rheumatol. 2009;28: 1431-1435.
29. Karvonen-Gutierrez CA, Harlow SD, Jacobson J, Mancuso P, Jiang Y. 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. 2014;73: 883-889.
30. Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. Curr Med Chem. 2008;15: 1851-1862.
31. Ray A. Adipokine leptin in obesity-related pathology of breast cancer. J Biosci. 2012;37: 289-294.
32. Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307: 426-430.
33. Auguet T, Terra X, Porras JA, et al. Plasma visfatin levels and gene expression in morbidly obese women with associated fatty liver disease. Clin Biochem. 2013;46: 202-208.
34. Duan Y, Hao D, Li M, et al. Increased synovial fluid visfatin is positively linked to cartilage degradation biomarkers in osteoarthritis. Rheumatol Int. 2012;32: 985-990.
35. Wang H, Chu WS, Hemphill C, Elbein SC. Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. J Clin Endocrinol Metab. 2002;87: 2520-2524.
36. Nohira T, Nagao K, Kameyama K, et al. Identification of an alternative splicing transcript for the resistin gene and distribution of its mRNA in human tissue. Eur J Endocrinol. 2004;151: 151-154.
37. Van Spil WE, Welsing PM, Kloppenburg M, et al. Cross-sectional and predictive associations between

plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. Osteoarthritis Cartilage. 2012;20: 1278-1285.
38. Schaffler A, Ehling A, Neumann E, et al. Adipocytokines in synovial fluid. JAMA. 2003;290: 1709-1710.
39. Braun HJ, Gold GE. Diagnosis of osteoarthritis: imaging. Bone. 2012;51: 278-288.
40. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;26: 355-369.
41. Dumond H, Presle N, Terlain B, et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum. 2003;48: 3118-3129.
42. Snelling SJ, Bas S, Puskas GJ, et al. Presence of IL-17 in synovial fluid identifies a potential inflammatory osteoarthritic phenotype. PLoS One. 2017;12: e0175109.
43. Gomez R, Lago F, Gomez-Reino J, Dieguez C, Gualillo O. Adipokines in the skeleton: influence on cartilage function and joint degenerative diseases. J Mol Endocrinol. 2009;43: 11-18.
44. Li XC, Tian F, Wang F. Clinical significance of resistin expression in osteoarthritis: a meta-analysis. Biomed Res Int. 2014;2014: 208016.
45. Lubkowska A, Radecka A, Bryczkowska I, Rotter I, Laszczynska M, Dudzinska W. Serum Adiponectin and Leptin Concentrations in Relation to Body Fat Distribution, Hematological Indices and Lipid Profile in Humans. Int J Environ Res Public Health. 2015;12: 11528-11548.
46. Agilli M, Ekinci S. Effect of leptin on the relationship between body weight and knee osteoarthritis--a methodologic approach: comment on the article by Fowler-Brown et al. Arthritis Rheumatol. 2015;67: 1141.
47. Calvet J, Orellana C, Gratacos J, et al. Synovial fluid adipokines are associated with clinical severity in knee osteoarthritis: a cross-sectional study in female patients with joint effusion. Arthritis Res Ther. 2016;18: 207.
48. Numan AT, Al-Joda AM, Jawad NK. Relationship between Serum Visfatin and Obesity in Lead-Exposed Obese Subjects and Patients with Osteoarthritis. Health. 2016;08: 318-324.
49. Westerbacka J, Corner A, Tiikkainen M, et al. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. Diabetologia. 2004;47: 1360-1369.
50. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med. 2009;6 Suppl 1: 60-75.
51. Stannus OP, Jones G, Quinn SJ, Cicuttini FM, Dore D, Ding C. The association between leptin, interleukin-6, and hip radiographic osteoarthritis in older people: a cross-sectional study. Arthritis Res Ther. 2010;12: R95.
52. Fioravanti A, Giannitti C, Cheleschi S, Simpatico A, Pascarelli NA, Galeazzi M. Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis. Int J Biometeorol. 2015;59: 1691-1700.
53. Cuzdan Coskun N, Ay S, Evcik FD, Oztuna D. Adiponectin: is it a biomarker for assessing the disease severity in knee osteoarthritis patients? Int J Rheum Dis. 2015.
54. Thirunavukkarasu K, Pei Y, Wei T. Characterization of the human ADAMTS-5 (aggrecanase-2) gene promoter. Mol Biol Rep. 2007;34: 225-231.
55. Bao JP, Chen WP, Feng J, Hu PF, Shi ZL, Wu LD. Leptin plays a catabolic role on articular cartilage. Mol Biol Rep. 2010;37: 3265-3272.
56. Huang K, Wu LD. Suppression of aggrecanase: a novel protective mechanism of dehydroepiandrosterone in osteoarthritis? Mol Biol Rep. 2010;37: 1241-1245.
57. El-Dein Farag A, Machaly S, Sultan W, Soliman N, Al-Harrass M, El-Ghaweet A. Adiponectin in patients with knee osteoarthritis. Benha Medical Journal. 2016;33: 133-141.
58. Junker S, Frommer KW, Krumbholz G, et al. Expression of adipokines in osteoarthritis osteophytes and their effect on osteoblasts. Matrix Biol. 2016.
59. Lago R, Gomez R, Otero M, et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage. 2008;16: 1101-1109.
60. Choi HM, Lee YA, Lee SH, et al. Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediators. Arthritis Res Ther. 2009;11: R161.
61. Filkova M, Liskova M, Hulejova H, et al. Increased serum adiponectin levels in female patients with erosive compared with non-erosive osteoarthritis. Ann Rheum Dis. 2009;68: 295-296.
62. Moschen AR, Kaser A, Enrich B, et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol. 2007;178: 1748-1758.

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