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Plasma Leptin and Adiponectin Levels and Disease Severity in Primary Knee Osteoarthritis

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ABSTRACT

Introduction and aim: Osteoarthritis (OA) is the commonest degenerative and painful articular disease. It is a significant cause of disability. Early diagnosis is crucial and searching for biomarkers is continuing. The current work aimed to assessment the plasma leptin and adiponectin concentrations in patients with primary knee osteoarthritis (OA), and to explore the relationship of leptin and adiponectin with OA severity

Methodology: Forty patients with primary knee osteoarthritis from both sexes who fulfilled ACR criteria for diagnosis of knee OA were enrolled. Other healthy subjects were included as a control group. Patients were sassed by history taking, clinical examination, radiological and laboratory investigations. WOMAC questionnaire was used to evaluate a patient's functions.

Results: Both study and control groups were comparable as regards to patient demographics, except their weight, height and body mass index (BMI). Obesity, hypertension, tenderness, pain grade, limitation of joint movements and WOMAC score, Kellgren Lawrence radiological criteria, leptin and adiponectin were increased in study when compared to control group. There was significant, positive, moderate correlation between leptin and BMI ($r=0.557$, $p < 0.001$). Higher leptin was associated with obesity and diabetes mellitus. Leptin serum levels revealed proportional, moderate, significant correlation with each of pain, stiffness and K-L criteria, while this correlation was powerful with physical function and total WOMAC score.

Conclusion: Leptin and adiponectin were increased in patients with osteoarthritis. Leptin alone is significantly associated with disease severity indices.

Keywords: **Biomarkers; Osteoarthritis; Leptin; Adiponectin; Diagnosis.**

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INTRODUCTION

Osteoarthritis (OA) is the commonest degenerative disease affecting joints. It is a significant cause of pain and disability in adults. OA is a disease of the whole joint. Its specific characteristics include degeneration of articular cartilage, sclerosis of subchondral bones, osteophyte development, synovial fluid inflammation, and degeneration of articular ligaments [1].

Among older adults (≥60 years of age), the symptomatic knee OA prevalence is up to 10.0% and 13.0% in males and females, respectively. This percentage is expected to be higher with aging of population or increased obesity [2].

Obesity epidemic affects every country on the world and usually associated with low grade inflammation. Recently, there was an increased trend of coexistence of OA and obesity. Obesity had been known as a major OA risk factor initiation and progression [3]. The effect of obesity on OA restricted to the biomechanical effects of weight and higher mass of fat. Increased weight could lead to cartilage degeneration by increasing mechanical load over the weight-bearing joints and/or by stimulation of mechanoreceptors located on the surfaces of chondrocytes. Mechano-receptor stimulation induce the production of different inflammatory mediators responsible for destruction of cartilage [4]. In addition, the non-weight bearing joints are increasingly affected by OA in obese subjects [5], raising the possible effects of other factors (e.g., adipokines in initiation and progression of the disease [6].

Adipokines are fundamental for different processes (e.g., cell differentiation and hematopoiesis). Adipokines function depends mainly on its concentration in the blood. Concentration above the optimal values are able to begin the process of low grade inflammation [7].

In knee OA, adipokines are produced by osteoblasts, chondrocytes, synovium and infrapatellar pads of fat. The adipokine concentrations usually correlate with cartilage degeneration. The white fatty tissues working as an active endocrine system and mainly secretes inflammatory mediators such as cytokines (e.g. Interleukins, tumor necrosis factor) and adipokines (e.g., resistin, adiponectin and leptin) [8].

Leptin induces a proinflammatory and destructive effect on cartilage by the production of interleukin-1β, matrix metalloproteinase 9 (MMP9) and MMP13 [9]. Additionally, adiponectin receptors have been recognized on the human chondrocytes suggesting a probable role in joint inflammation [10].

Generally, the diagnosis of OA is usually confirmed by radiological investigations. However, this usually happen late in the disease after remarkable destruction of cartilage. Biochemical markers could offer a potential alternative for earlier diagnosis of the disease even in non-symptomatic individuals. As adipokines play a crucial role in cartilage and bone homeostasis, its link with obesity, and its pro- or anti-inflammatory properties, adipokines could be a potential biomarker for the diagnosis of OA and an indicator of disease severity, but results were contradictory [11]. Thus, we carried the current work, aiming to investigate this role.

THE AIM OF THE WORK

The current study aimed was to measure plasma levels of leptin and adiponectin levels in primary knee OA, and to investigate the relationship of leptin and adiponectin with disease severity.

PATIENTS AND METHODS

Forty patients with primary knee osteoarthritis from both sexes who fulfilled ACR criteria for diagnosis of knee OA [12] were enrolled to participate in the study. Patients were recruited from a regular attendant at the outpatient rheumatology and rehabilitation clinics of Al-Azhar University hospitals, Damietta. Also, twenty apparently healthy subjects were enrolled in the study. All participants provided a written consent before inclusion in the study. The exclusion criteria were any joint condition other than primary knee OA, such as rheumatoid arthritis, gout, and trauma or surgery of the knee joint.

The patient assessment included history taking, general examination, detailed examination of the knee joint. Range of motion (ROM) had been determined in the prone position by the international standard goniometer, as described and validated previously [13].

In addition, pain assessment had been achieved by the use of the visual analogue scale as described elsewhere [14]. Furthermore, WOMAC questionnaire was used to assess the patient's functions [15].

It is a 24-item questionnaire with three subscales for pain (five items), stiffness (two items), and physical function (17 items). Finally, laboratory investigations had been carried out. First for basic laboratory investigations and specific laboratory investigations, that included leptin and adiponectin as described by Staikos *et al.* [16].

All participants were examined by plain X-ray anteroposterior standing and lateral views for both knees. All radiographs were interpreted by a single observer using the Kellgren and Lawrence criteria [17]. Besides, magnetic resonance imaging (MRI) was done by Achieva Philips 1.5 tesla. Patients are placed in the supine position with the knee placed in a closely coupled extremity coil. Multi-sequences MRI study for the knee joint was performed. Images were used to assess the features of knee OA. MRI findings were analysed as described by Argentieri *et al.* [18].

Data analysis: The collected data analyzed by statistical package for social science version 22 (IBM®,SPSS® Inc., USA). Numerical variables were expressed by mean and standard deviation (SD), while categorical data were presented as frequencies and percentages. Comparison between groups was achieved by one analysis of variance, independent samples (t) test, Chi square or 'Mann–Whitney' test, according to the type of data. P value < 0.05 was considered significant.

RESULTS

The present study included 40 patients with primary OA, 12 of them (30.0%) were males and 70.0% were females with no significant difference when compared to control group (40.0% were males and 60.0% were females). The age of studied subjects ranged from 52 to 73 years, with no significant difference between OA and control groups (66.62±5.45 vs 66.90±6.38 years, respectively). On the other side, there was a statistically significant increase of weight and BMI in OA when compared to control group (74.58±7.79 and 27.13±3.45 vs 68.70±7.68 and 24.38±2.89 successively). However, height was significantly decreased in OA versus control (1.66±0.03 vs 1.68±0.03, respectively). Comorbidities, e.g., obesity, smoking, diabetes mellitus, hypertension and cardiac disease were reported among 28.3%, 21.7%, 15.0%, 53.3% and 5.0% successively of all included subjects; and there was significant increase of obesity and hypertension among OA when compared to control group (37.5%, 70.0% vs 10.0%, 20.0%, respectively) (Table 1).

The tenderness elicited by firm digital pressure over the joint margin revealed a significant difference between study (OA) and control groups, where no tenderness at all was recognized in 13(65.0%) of control group compared to none in study group. In addition, patient complain of tenderness (grade-1) in 25% of OA compared to 35% of control group. In

addition, 57.5% and 17.5% of the OA group had grades-2 and 3, respectively compared to none of control group. Pain, assessed by visual analogue scale (VAS), there was a statistically significant increase of moderate and severe pain among study when compared to control group (67.5% and 27.5% vs 0.0% and 0.0% respectively). All patients in study group had pain (5.0% had mild pain), while 55% of control group had no pain and 45.0% had mild pain. The ROM examination revealed a statistically significant decrease of flexion ROM degree in the study group in comparison to the control group both on the right (111.50±10.87 vs 131.50±3.28) and the left (114.13±9.80 vs 128.75±4.25) sides. On the other side, knee extension showed non-significant difference between OA and the control groups on the right or the left sides (Table 2).

Regarding pain assessed by WOMAC questionnaire, it ranged from 0 to 20 and there was significant increase among OA when compared with the control group (9.73±3.42 vs 2.85±1.69 respectively). In addition, stiffness ranged from 0 to 8 with significant increase among the OA group (3.83±1.85) vs (1.05±0.83) for the control group. Furthermore, physical function score ranged from 3 to 68, while total score ranged from 0 to 96 and there was significant increase of both physical function and total scores among study group (38.28±14.39, 51.83±18.41 respectively) in comparison to control group (9.05±3.53 and 12.95±4.19 with corresponding order).

Regarding Kellgren-Lawrence (K-L) criteria, there was a statistically significant difference between study and control groups. All subjects in the control group had grade-0 (i.e., normal joint); while 30.0%, 42.5%, 15.0% and 12.5% of patients in the OA group were of grades one, two, three, and four successively. The serum leptin (ng/ml) levels ranged from 18 to 90; and there was significant increase among OA when compared with control group (42.22±18.11 vs 28.60±5.04 respectively). In addition, serum adiponectin (µg/ml) ranged from 10 to 81 with significant increase among study when compared with control group (32.52±15.44 vs 15.50±3.63 respectively) (Table 3).

In the present work, articular cartilage score (by MRI examination) ranged from 0 to 4 and there was significant increase of the score among study when compared with control group (2.80±1.17 vs 0.40±0.50 respectively). Similarly, there was significant increase of marginal osteophytes score among study when compared with control group (2.40±1.44 vs 0.20±0.41 respectively). Among the current work, there was significant, proportional (positive), moderate correlation between leptin and BMI ($r=0.557$, $p < 0.001$). Otherwise, no significant correlation was found between leptin and patient age. In addition, there was no significant correlation between adiponectin with age or BMI. Among the study group, leptin serum levels revealed proportional, moderate, significant correlation with each of pain, stiffness and K-L criteria, while this correlation was powerful with physical function and total WOMAC score. On the other side, adiponectin did not correlate with any of WOMAC domains, total WOMAC or K-L criteria (Table 4).

Regarding relation between leptin and associated comorbidities in the OA group, there was significant increase of leptin in obese when compared with non-obese patients (53.87±23.41 vs 35.24±8.85 respectively). Also, there was significant increase of leptin in diabetics when compared with non-diabetics (55.57±27.15 vs 39.39±14.65 respectively). On the other side, adiponectin had no significant association with obesity, smoking, diabetes, hypertension or cardiac disease (Table 5). In the study group, MRI articular cartilage score was significantly correlated with marginal osteophyte score, leptin, all WOMAC score domains and total score and K-L criteria. The powerful correlation was with K-L criteria followed by total WOMAC score. In addition, MRI marginal osteophytes score correlated with stiffness of WOMAC score. Otherwise, no significant correlation was found (Table 6).

Finally, there was no significant difference between cases with effusion and those without effusion regarding serum levels of adiponectin or leptin.

Table (1): Comparison between study and control groups are regard to patient criteria and associated comorbidities

Parameter		OA group	Control group	*Test*	*P value*
Subject gender	Male	12(30.0%)	8(40.0%)	0.60	0.43(ns)
	Female	28(70.0%)	12(60.0%)		
Subject age (year)		66.62±5.45	66.90±6.38	0.17	0.86(ns)
Weight (kg)		74.58±7.79	68.70±7.68	*2.76*	*0.008**
Height (m)		1.66±0.03	1.68±0.03	*2.23*	*0.029**
BMI (kg/m²)		27.13±3.45	24.38±2.89	*3.07*	*0.003**
Associated comorbidity	Obesity	15(37.5%)	2(10.0%)	*4.96*	*0.026**
	Smoking	11(27.5%)	2(10.0%)	*2.40*	*12(ns)*
	Diabetes	7(17.5%)	2(10.0%)	*0.58*	*0.44(ns)*
	Hypertension	28(70.0%)	4(20.0%)	*13.39*	*0.001**
	Cardiac disease	2(5.0%)	1(5.0%)	*0.01*	*1.0(ns)*

Table (2): Comparison between study and control groups are regard to knee tenderness grade, pain severity, and range of motion (ROM)

			Group				Statistics	
			OA (40)		Control (20)			
			n	%	n	%	Test	p
Tenderness grade	0 (No tenderness)		0	0.0%	13	65.0%	41.47	<0.001*
	1(Patient compliant of tenderness)		10	25.0%	7	35.0%		
	2(Tenderness and winces)		23	57.5%	0	0.0%		
	3(Tenderness, winces and withdraws the joint)		7	17.5%	0	0.0%		
Pain grade	No pain		0	0.0%	11	55.0%	52.63	<0.001*
	Mild (1-3)		2	5.0%	9	45.0%		
	Moderate (4-7)		27	67.5%	0	0.0%		
	Severe (>7)		11	27.5%	0	0.0%		
ROM	Right knee	Flexion	111.50±10.87		131.50±3.28		8.02	<0.001*
		Extension	5.75±9.31		1.75±2.45		1.88	0.07
	Left knee	Flexion	114.13±9.80		128.75±4.25		6.36	<0.001*
		Extension	4.25±7.03		2.25±2.55		1.22	0.22

Table (3): Comparison between study and control groups are regard to serum levels of leptin and adiponectin

		Mean	S D	Min.	Max.	t	p
Leptin (ng/ml)	OA	42.22	18.11	22.00	90.00	3.28	0.002*
	Control	28.60	5.04	18.00	39.00		
Adiponectin (µg/ml)	OA	32.52	15.44	10.00	81.00	4.84	<0.001*
	Control	15.50	3.63	10.00	22.00		

Table (4): The correlation between each leptin and adiponectin with patient age, BMI and disease duration among the study group

		Leptin		Adiponectin	
		r	p	r	p
Age		-0.129	0.429	0.21	0.20
BMI		0.557**	0.000	-0.079	0.62
WOMAC score	Pain	0.692**	<0.001	0.003	0.986
	Stiffness	0.596**	<0.001	0.049	0.764
	Physical function	0.724**	<0.001	-0.108	0.505
	Total	0.754**	<0.001	-0.079	0.627
K-L criteria		0.692**	<0.001	-0.080	0.625

**: Correlation is significant at the 0.01 level (2-tailed). *: Correlation is significant at the 0.05 level (2-tailed).

Table (5): Relationship between leptin and adiponectin to associated comorbidity among the study group

		Leptin		P value	Adiponectin		P value
		Mean	SD		Mean	SD	
Obesity	Obese	53.87	23.41	0.001*	31.86	14.52	0.83
	Non-Obese	35.24	8.85		32.92	16.24	
Smoking	Smoker	45.00	25.66	0.55	37.72	18.70	0.19
	Non-smoker	41.17	14.76		30.55	13.87	
Diabetes mellitus	Diabetic	55.57	27.15	0.030*	35.85	18.81	0.53
	Non-diabetic	39.39	14.65		31.81	14.87	
Hypertension	Positive	44.46	21.04	0.23	31.07	14.67	0.37
	Negative	37.00	5.86		35.91	17.28	
Cardiac disease	Positive	63.50	37.48	0.09	18.00	8.48	0.17
	Negative	41.11	16.80		33.28	15.40	

Table (6): The correlation between MRI and each of leptin, adiponectin and disease severity indices among study group

		MRI articular cartilage score		MRI marginal osteophytes score	
		r	p	r	p
MRI articular cartilage score				0.321*	0.043
MRI marginal osteophytes score		0.321*	0.043		
Adiponectin		-0.081	0.621	-0.229	0.155
Leptin		0.429**	0.006	0.222	0.168
WOMAC score	Pain	0.505**	0.001	0.095	0.558
	Stiffness	0.611**	<0.001	0.352*	0.026
	Physical function	0.590**	<0.001	0.236	0.143
	Total	0.617**	<0.001	0.238	0.140
K-L criteria		0.710**	<0.001	0.260	0.105

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Very few studies have been carried out to investigate the effects of adipocytokines on the different clinical and radiological features of knee OA. Thus, the present work was designed to estimate levels of serum leptin and adiponectin in OA patients and to investigate the possible correlation to disease severity.

Results of the present study revealed significant increase of BMI, hypertension, obesity, tenderness, WOMAC domains and significant decrease of knee flexion ROM among study group. Furthermore, there was a significant correlation between leptin and each of BMI and WOMAC domains, with significant increase of leptin among diabetics when compared with non-diabetics among study group. On the other side, adiponectin showed no significant association or correlations with studied variables.

These results are in line with de Boer *et al.* [19] who reported that, BMI, radiological joint damage and all serum adipocytokines were higher in OA than in controls.

Besides, Honsawek *et al.* [20] reported significant increase of adiponectin in mild and moderate grades of OA than controls, but decreased concentration in severe grades of OA.

Kroon *et al.* [21] studied the role of adipokines in OA. They reported higher leptin levels with higher grades of OA. But, such association could not be found with adiponectin (in the present work, both adipokines were increase in OA when compared with controls). Leptin suggested to mediate the link between obesity and OA. Generally, effects were more pronounced in women than in men (no significant difference in the present study).

Results of the present work agree with Richter *et al.* [22] who reported that, there was a higher concentration of leptin in the obese subjects, which was correlated with BMI and total body fat.

In addition, Berry *et al.* [23] reported a significant correlation between disease severity and serum leptin concentrations.

Richter *et al*. [22] in patients with normal-weight, found a correlation between leptin concentration and the severity of the radiographic manifestations in the knee joints. These radiographic changes also correlated with the BMI of the patient. This indicates the value of the leptin concentrations is the assessment of radiological features in less advanced knee OA.

Many trials indicate that the concentration of leptin in synovial fluid could be more significant for diagnosis of joint destruction than its serum concentrations. For example, Simopoulou *et al*. [24] reported a higher leptin concentration in the synovium than in the serum of patients with knee OA. In addition, local leptin concentrations were higher in obese patients.

In agreement with the present work, Zhang *et al*. [25] reported that, serum leptin concentrations are clearly higher in OA compared with non-OA. In addition, leptin concentrations are strongly associated with radiographic features of OA.

Moreover, leptin concentrations showed a significant correlation with different obesity parameters [26]. Fowler-Brown *et al*. [27] proved that serum leptin could mediate about half of the total destructive effect of higher BMI on the knee OA.

Previous literature yields conflicting results regarding the association between higher leptin concentration and the radiographic severity features of OA. Some reported positive correlation between leptin levels in serum/plasma, and OA radiographic severity [16].

Others failed to show any association between these two parameters [28].

One meta-analysis of 11 studies supported the role of increased leptin concentrations association with the disease severity, particularly among females [25].

Another longitudinal survey of 511 patients reported that high basal serum leptin concentration in premenopausal females were predictors of poor mobility-based functions [29].

Most of the previous trials supporting the role of leptin as a pro-inflammatory and catabolic agent in cartilage metabolism, exerting this action alone or in a synergistic manner with other pro-inflammatory factors. Thus, increasing the risk for OA [30].

On the opposite side, there are few studies reporting a protective role of leptin in OA, through anti-inflammatory and anabolic actions. Gross *et al*. found that the leptin-free form was negatively correlated with interleukin-6 (IL-6), suggesting that, the free form may reduce inflammation [31].

Another study showed that leptin may suppress tumor necrosis factor (TNF)-α-stimulated death of articular chondrocytes [32].

To explain, leptin may play a dual action on OA in both pro-/anti-inflammatory and catabolic/anabolic ways. Perhaps, stimulated catabolic/ pro-inflammatory actions and impaired anabolic/anti-inflammatory effects could lead to a harmful effect overall. Further studies are required to investigate the probable metabolic balance of leptin on knee OA [33].

Clinical studies also gave conflicting results regarding the association between serum concentration of adiponectin and knee OA. A positive correlation between adiponectin concentrations and the progress of OA, was reported [34]. However, Honsawek and Chayanupatkul [20] reported an inverse correlation between serum adiponectin and the severity of degenerative changes in knee OA.

Koskinen *et al*. [35] also found that adiponectin levels were higher in patients with advanced OA than in less severe disease. This suggests the association between adiponectin and cartilage destruction in OA.

Additional support for our findings is provided by the work of Laurberg *et al*. [36], who showed elevated adiponectin concentrations in OA than healthy subjects.

Results of the present work are supported by study of Klein-Wieringa *et al*. [37], who revealed a significant correlation between circulating adiponectin with joint erosions in rheumatoid arthritis.

Other studies reported different findings on the link between adiponectin levels and radiographic features. The work of Honsawek *et al*. [20], showed lower plasma and synovial adiponectin concentrations with severe knee OA. This association was lost for plasma concentration after adjusting for gender, age and BMI. These differences ascribed to different radiographic scales.

Otherwise, Yusuf *et al*. [38] reported that higher values of the plasma adiponectin are associated with a reduced risk for progression of hand OA during a 6-year follow-up. This study is contradictory to results of the current work. The contradiction may be explained by different factors: variable methods used to quantity adiponectin, differences in patient characteristics and differences in the pathophysiology of knee and hand OA. It is also likely that the significance of adiponectin differs according to the stage and severity of OA.

A negative correlation between adiponectin and BMI had been reported in a previous study [39]. However, other clinical studies did no confirm such correlation [40], as in the present work.

This could be attributed to the variability of different factors regulating adiponectin and the production of adiponectin by other tissues other than white adipose tissues [39].

In a meta-analysis, Tang *et al*. [10] reported that, expression level of adiponectin was higher in OA than in healthy subjects. This result support a previous study reported the key role of adipose tissue metabolism in the development of OA [41] and the adiponectin might play a role in OA pathogenesis. However, it is still a matter of debate whether adiponectin exerts a protective or a harmful role. Some researchers considered its function to be a pro-inflammatory mediator that led to OA, while others advocated the opposite opinion.

In clinical trials, the association between adiponectin and severity of the OA is also controversial. Most researchers reported a protective role adiponectin against OA on the basis of its negative correlation with the disease progression [42].

In short, results of the present study revealed that, both leptin and adiponectin were significantly increased in patients with osteoarthritis than healthy controls. Leptin alone is significantly associated with disease severity indices, and no correlation was found between adiponectin and disease severity indices.

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None to be declared.

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