Shafa Ortho J. 2017 May; 4(2):e10733. doi: 10.5812/soj.10733.

Published online 2017 April 12. **Research Article**

Some Adipose Derived Hormones in Association with the Risk of Knee Osteoarthritis

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Received 2017 January 28; **Revised** 2017 March 05; **Accepted** 2017 April 01.

Abstract

Background: Knee osteoarthritis (OA) is the most common form of arthritis and is the major cause of pain and disability in the elderly. The relationship between obesity and increased risk of knee osteoarthritis was known for many years. Since then, many studies have shown the relationship between knee osteoarthritis and obesity.
Objectives: In this study, we tried to evaluate whether compared to weight, the adipose tissue has a stronger correlation with the occurrence of knee osteoarthritis.
Methods: In a cross-sectional study that was a part of the Fasa knee osteoarthritis registry (FOAS), 131 patients with OA were sex matched with 262 patients in the control group. Serum samples of the patients, the Western Ontario and McMaster universities arthritis index (WOMAC) questionnaire and demographic data were collected. Leptin and adiponectin as hormones secreted by the adipose tissue were measured.
Results: Weight, body mass index (BMI), and waist circumference (WC) were significantly different between the two groups ($P < 0.001$). The Kellgren and Lawrence (K&L) score was significantly higher among the patients ($P < 0.001$). Pain levels in patients with OA were also significantly higher compared to those in the control group ($P < 0.001$). Both leptin and adiponectin concentrations were higher in the OA patients. Adiponectin had a negative relationship with BMI in the OA group ($r = 0.570$, $P < 0.001$), but leptin had a positive relationship with BMI ($r = 0.781$, $P < 0.001$). In the OA group, both adipokines had higher levels in female patients compared to male patients.
Conclusions: The results of the current study showed that levels of hormones secreted from the adipose tissue, in people with knee OA, were higher compared to the control group, indicating the possible effect of these hormones on the process of osteoarthritis. Finally, we showed that after adjusting for age, sex, and BMI, leptin and adiponectin are significantly correlated with the amount of pain indicating higher levels of leptin and adiponectin lead to increased pain.

Keywords: Knee Osteoarthritis, Leptin, Adiponectin, Weight

1. Background

Knee osteoarthritis (OA) is one of the most disabling diseases in old age, and it is estimated that 25% of people over the age of 55 years have permanent pain and about 10% have debilitating pain in the knee (1, 2). Osteoarthritis wastes 2,118,000 years of the life of human societies annually (3). Primary reasons that can be cited for developing osteoarthritis are gender, weight, articular injuries, genetic factors, and metabolic disorders (4, 5), but the etiology of the disease is not yet fully understood (6). Arthritis symptoms usually appear after the age 45 - 50. In 1986, the American association of rheumatology defined osteoarthritis in the form of "a group of heterogeneous conditions that lead to articular complications and symptoms, and are associated with articular cartilage defects and make changes in the underlying bone in the articulation joint margin (7)." Osteoarthritis as a major cause of pain and disability in the elderly is the most common form of arthritis (8). With the new findings regarding the pathophysiology of the disease, today, we know this complication a state related to age, genetics, trauma and metabolic conditions.

Incidence of knee osteoarthritis is not very accurate in Iran, but according to the study of the community oriented program for the control of rheumatic diseases (COPCORD) conducted by Forghanizadeh et al. in the region of Fasham, its prevalence was 17.87% including 86.4% localized, and 13.6% generalized (9). Metabolic conditions such as adipokines, high blood sugar, hormone changes,

and free radicals play a major role in the development and advancement of the disease (10). They lead to these complications in middle age (45 - 65 years old) and bring pain and disability. The results indicate that 59% of the patients with knee osteoarthritis have metabolic syndrome, while this prevalence rate is about 23% for people without osteoarthritis (11). Studies also show that people with metabolic syndrome are usually suffering from knee osteoarthritis in younger ages; they have more general symptoms and experience more pain than those without metabolic syndrome (12, 13).

The relationship between obesity and increased risk of knee osteoarthritis was known for many years. In 1988, the data from the national health and nutrition examination survey (NHANES) showed that obese women and men had increased risk of knee osteoarthritis about respectively 4 and 5 times more than nonobese people (14). Since then, many studies have shown the relationship between knee osteoarthritis and obesity (6, 15).

Although the exact mechanism of the relationship between knee osteoarthritis and obesity is not yet fully understood, some studies reported the existence of mechanical and metabolic factors in this regard (16). In terms of mechanical factors, articulations, especially cartilage and subchondral bones are exposed to mechanical stress (17). While the overweight imposed it can justify the increased risk of osteoarthritis in knee and hip articulations, but explaining the relationship between body mass index (BMI) and osteoarthritis of the hand is very difficult (18). In addition, it has been shown that reducing the amount of body fat has better effects than weight loss in the management of patients with knee osteoarthritis (19). A study conducted by Dumond et al. presented the first evidence of the key role of leptin in knee osteoarthritis, and started a direction for further study of adipokines as the metabolic link between obesity and knee osteoarthritis (20).

2. Objectives

It seems that, compared to weight, the adipose tissue has a stronger correlation with the occurrence of osteoarthritis. Accordingly, in this study, we aimed to examine the relationship between some hormones secreted from adipose tissues, which indirectly represent the amount of adipose tissue and also provide the metabolic characteristics of adipose tissue in the incidence of knee osteoarthritis.

3. Methods

3.1. Specifications of the Patients

This study was a part of the registry of patients with knee osteoarthritis in Eastern part of Fars Province, which was conducted with the grant of Fasa University of Medical Sciences. In this study, 131 patients with knee osteoarthritis were registered, twice that number were selected in the control group from patients referred to the orthopedic clinic of the University, and inclusion criterion of the control group was the lack of knee osteoarthritis radiographic symptoms [Kellgren and Lawrence (K & L) = 0]. The patients in the control group were matched by gender. Patients who used anti-inflammatory drugs or steroids, or weight loss drugs, or those who has attempted to reduce the weight in the past three months were excluded from the study. Blood samples were taken from all patients in one day at the central laboratory of the University.

Demographic information and the individuals' Western Ontario and McMaster Universities arthritis index (WOMAC) can be seen in Table 1. The present study was conducted based on the declaration of Helsinki and approved by the university ethics committee. Informed consent was obtained from all the patients of the study.

3.2. Measures

Anthropometric evaluations were performed on subjects with light cloths and bare foot. The waist circumference (WC) was measured using an inelastic tape at midpoint of the inferior border to lowest ribs to the anterior superior iliac spine, after a normal expiration. Also, height was measured to its nearest 0.1 cm using a stadiometer (Seca 767, Japan) and weight was measured to its nearest 0.1 kg using a digital scale (Seca 767, Japan). Waist circumference was also measured with minimal clothing and using the world health organization criterion (21). The BMI was calculated as weight (Kg) divided by the squared height (m^2).

Serum samples were tested for leptin and adiponectin using a commercial enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, USA) according to the manufacturer's recommendations. The sensitivity values of the ELISA kit for the detection of leptin and adiponectin were 20 pg/mL and 12 pg/mL, respectively.

3.3. Statistical Analysis

Data were analyzed using the SPSS version 22 (SPSS Inc, Chicago, IL, USA). All the variables are displayed as means $\pm$ standard deviations or percentage and frequency where appropriate. Our statistical inference was based on a 95% confidence interval (CI) and a P value of 5%.

Table 1. Comparison of Demographic Variables Between Osteoarthritis Patients and the Control Group for Both Genders

	Male			Female		
	Case (n = 24)	Control (n = 48)	P Value	Case (n = 107)	Control (n = 214)	P Value
Age, y	57 ± 5	57 ± 6	0.681	56 ± 8	55 ± 7	0.427
Weight	89.00 ± 7.65	75.77 ± 9.05	< 0.001	83.57 ± 11.97	73.56 ± 7.42	< 0.001
Waist	98.00 ± 6.80	90.61 ± 6.97	< 0.001	90.12 ± 2.75	86.06 ± 3.64	< 0.001
BMI	28.73 ± 2.20	25.77 ± 2.83	< 0.001	28.14 ± 2.18	26.02 ± 2.28	< 0.001
K&L	2.84 ± 0.34	0	< 0.001	2.95 ± 0.54	0	< 0.001
WOMAC	13.59 ± 2.79	6.56 ± 3.26	< 0.001	15.45 ± 3.25	5.26 ± 2.63	< 0.001
Leptin	42.54 ± 7.97	31.9 ± 8.09	< 0.001	50.49 ± 14.24	31.51 ± 7.29	< 0.001
Adiponectin	20.77 ± 4.68	9.3 ± 5.47	< 0.001	21.28 ± 6.16	11.12 ± 3.72	< 0.001

Abbreviations: BMI, body mass index; K&L, Kellgren and Lawrence; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Comparison of variables between the OA and control groups was performed using t test for quantitative and the chi-square test for qualitative variables. Logistic regression was used to examine the effect of metabolic syndrome and its component on OA. Linear regression was used to find WOMAC score correlates.

4. Results

4.1. Participants' Characteristics

Table 1 shows demographic characteristics of 131 patients with knee OA and 262 participants in the control group separately for males and females. Female patients were younger than females in the control group (P = 0.017). Weight, BMI, and WC were significantly different between the two groups (P < 0.001). The Kellgren and Lawrence score was significantly higher among patients (P < 0.001). Pain levels in patients with OA were also significantly higher compared to those in the control group (P < 0.001).

4.2. Adipokine Associations

Regarding hormones secreted by the adipose tissue (leptin and adiponectin), concentrations of all the hormones were higher in knee OA patients (Table 1).

In the linear regression model, after adjusting for age, sex and BMI, both of the hormones had a significant and positive association with OA (B: 12.56 and B: 10.78 for leptin and adiponectin, respectively; P < 0.001) (Table 2).

Adiponectin had a negative relationship with BMI in the OA group (r = 0.570, P < 0.001), but leptin had a positive relationship with BMI (r = 0.781, P < 0.001). In the OA group, both adipokines had higher levels in female patients compared to male patients.

In the control group, leptin had a significant relationship with BMI (but this relationship was weaker compared to that in the OA group) (Figure 1).

4.3. Relationship Between the Pain Level and Adipokines

Results suggested that there was a significant relationship between leptin and adiponectin levels and pain in OA patients (Table 3).

5. Discussion

The results of our study clearly indicated a higher level of hormones secreted from adipose tissue in knee osteoarthritis patients compared to the control group without radiographic complications of articular damage independent of BMI, age and gender. Since the BMI between the two groups was different, we tried to adjust all results for BMI. Both leptin and adiponectin were significantly associated with BMI levels; it was quite predictable due to the higher amount of adipose tissue in people with a higher BMI.

There are small number of considerable studies exploring the relationship between adipose tissue hormones and knee osteoarthritis compared with the control group. Major studies have been conducted on the hand articulation osteoarthritis to reduce the influence of mechanical stress; or a small number of factors have been studied (22, 23). This is while the incidence of osteoarthritis in the knee articulation is much more than the other articulations.

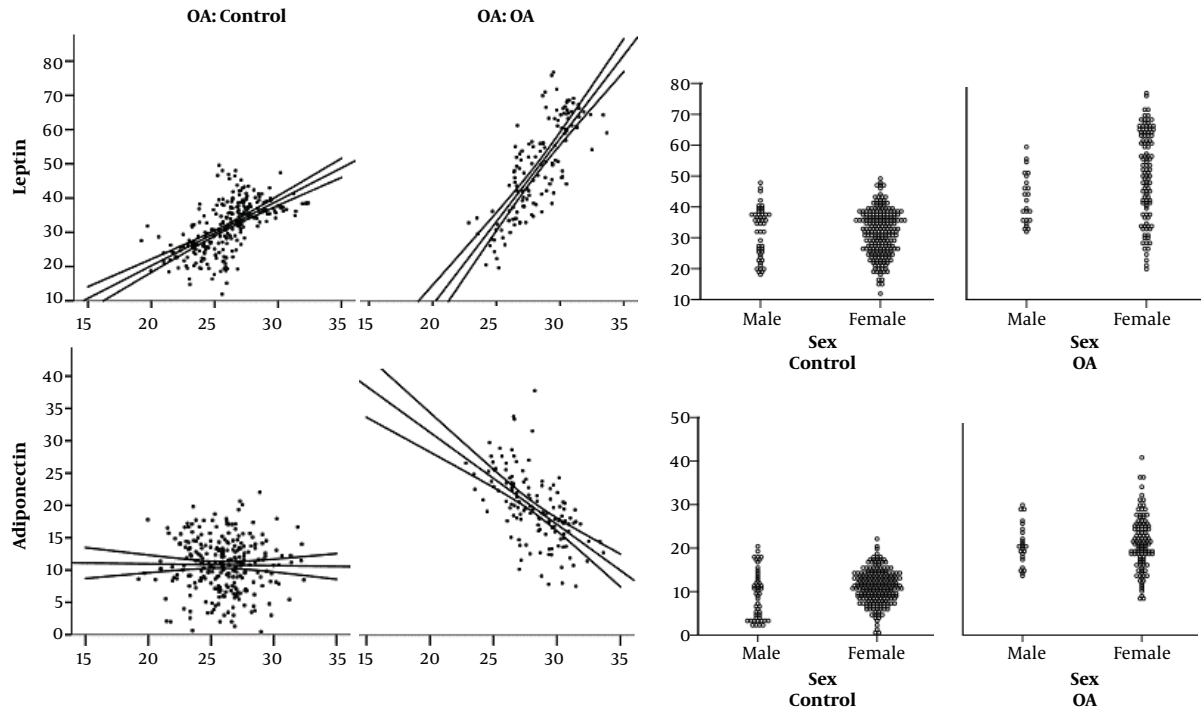
In the Framingham study, 37% of people over 60 years had conflict in the knee, while this percentage for the articulations of hand and hip were around 27% and 9%, respectively (24). So, perhaps more accurate findings can be obtained from addressing the knee articulation. Our study

Table 2. Linear Regression Between OA and Each Adipocin After Adjusting Sex, Age and BMI Effect

	Leptin (Adj. R2 = 0.676)		Adiponectin (Adj. R2 = 0.551)	
	B[a]	P Value	B	P Value
State (OA)	12.562	< 0.001	10.784	< 0.001
Gender (female)	0.749	0.468	2.145	0.001
Age, y	0.220	< 0.001	-0.105	0.001
BMI	2.402	< 0.001	-0.292	0.011

Abbreviations: BMI, body mass index; OA, Osteoarthritis.
[a]Unstandardized Regression Coefficients beta.

Figure 1. Relationship Between Serum Adipokine Levels and Body Mass Index and Gender in OA Patients and Controls



Statistics are Obtained from Pearson's Correlation Analysis.

showed that the relationship between increased leptin and BMI in patients with knee osteoarthritis is much stronger and higher than the patients in the control group; while the relationship between adiponectin and BMI in patients with knee osteoarthritis showed an inverse relationship. Unlike adiponectin, leptin in OA women is more than men, while no significant difference was seen between men and women in the control group.

Articular cartilages are complex biological tissues made by the chondrocytes; as a result, conditions such as aging, illness or injury suffer from metabolic changes. According to epidemiological studies, the effect of increased mechanical stress imposed on weight-bearing articulations due to overweight and obesity has long been considered as the main cause of damage to the articulations. However, it seems that in addition to weight, other factors are also involved in the damage. Hormones secreted from the adipose tissue known as adipokines are responsible for at least part of this relationship (14, 25). Explorations of these messenger combinations are not very old and date back to 20 years age at most; and the adipose tissue is known as a tissue containing endocrine proper-

Table 3. Linear Regression Between WOMAC and Each Adipocin After Adjusting Sex, Age and BMI

	WOMAC (Adj. R2 = 0.730)		WOMAC (Adj. R2 = 0.730)	
	B (SE)[a]	P Value	B (SE)[a]	P Value
State (OA)	8.66 (0.43)	< 0.001	10.14 (0.49)	< 0.001
Gender (female)	-0.73 (0.40)	0.065	-0.52 (0.40)	0.194
Age, y	0.05 (0.02)	0.012	0.05 (0.02)	0.008
BMI	0.11 (0.08)	0.194	0.20 (0.07)	0.004
Leptin	0.05 (0.02)	0.014	-	-
Adiponectin	-	-	-0.08 (0.03)	0.009

Abbreviations: BMI, body mass index; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
[a] BUnstandardized Regression Coefficients bet.

ties (26). Leptin was discovered in 1994 as the first member of this family (27). Today, there is a view that the molecules secreted from adipose tissue may play a pivotal role in the pathogenesis of obesity, such as pushing towards metabolic syndrome, inflammatory conditions or autoimmune diseases. It has been shown that adipokines may also have a multidimensional role, and can affect the pattern of eating, energy consumption, glucose metabolism, insulin sensitivity, oxidation of fatty acids and also regulating heart function, fertility, or inflammatory responses (28). In addition to the metabolic field, recent studies have shown the relationship between these molecules and bones' biology. Studies show the effect of these adipokines on bone mass metabolism on one hand, and the relationship between body fat mass with bone tissue, on the other hand. Meanwhile, the relationship must be seen mutual because adipose tissue have effects on bone mass and bones' metabolism (29) on one hand, and mutually, bone mass have effects on the body energy metabolism through some intermediaries such as osteocalcin, on the other hand (30). The relationship between adipokines and cartilage is also another important issue that should be addressed in this context.

Nowadays, obesity is a major risk factor for diseases associated with cartilage (31). The mechanism by which obesity affects the structure and symptoms of cartilage disease is not known accurately, but it can be due to systemic and also local inflammations resulting from the increase in adipose tissue and adipokines levels, especially leptin. Although it was previously thought that only adipocytes are capable of producing leptin, recent studies show that cells such as osteoblasts and chondrocyte are also able to synthesize and release leptin, which suggests the importance of local production of leptin in addition to the leptin released by the infrapatellar fat (32-34). For example, high concentrations of leptin have been reported in the articular fluid, and cartilage of the patients with cartilage diseases (35). In obese people, increased leptin circulation can be largely attributed to systemic mild inflammation listed (36, 37). In this sense, it makes obese people prone to not only the cardio-metabolic disease, but also inflammatory degenerative diseases such as osteoarthritis. Hence, it is assumed that leptin is the link between obesity metabolic disorders and increased risk of osteoarthritis that exerts a deleterious effect on articular cartilage along with other preinflammatory cytokines. In fact, ex vivo studies have been shown that leptin facilitates the production of proinflammatory factors in osteoarthritis cartilage through the activation of transcription factors such as NF-B and JNK (38). In addition, intra-articular injection of leptin to mice can significantly increase gene expression and protein levels of MMP-2 and -9, cathepsin D and two important aggrecans of ADAMTS-4 and -5, and reduce the level of basic fibroblast growth factor, which suggests a catabolic effect of leptin on cartilage metabolism (39). It has also been shown that leptin has a damaging effect on chondrocytes proliferation through inducing the expression of interleukin-1 and MMP-9 and -13 (40). Another in vivo study examining the relationship between leptin concentration of articular fluid and the severity of osteoarthritis disease showed that leptin concentration of intra-articular fluid is closely related to the severity of the cartilage disease in the radiographic image. Thus, it is suggested that leptin may be effective as a marker for quantitative assessment of osteoarthritis (35). Studies have shown that the cultured articular cells and also human articular chondrocyte have leptin LRb receptors (41); this amount of receptor expression in advanced cases of the osteoarthritis disease increases compared to the mild cases (40). The fact that leptin gene expression of cartilage and the leptin level of the articular fluid is closely connected with the BMI, and leptin level in the articular fluid is higher than the serum level (32) suggests that lep-

tin may be the link between obesity and osteoarthritis (40).

Our results were in line with the study conducted by de Boer et al. (2012). In this study which was conducted on 30 patients with knee end stage, higher levels of leptin and adiponectin were observed in the OA group compared with the control group (42). Recently, most of the studies suggest that leptin plays a key role in the homeostasis of articular cartilage, and the destruction of articular cartilage in OA process. In a study conducted in 2003 (20), it was shown that leptin is also present in the articular fluid of people with osteoarthritis. It was also seen that with increasing severity of osteoarthritis and the articular cartilage destruction, leptin level was even higher. Also, some related studies reported the effects of leptin on facilitating the production of proinflammatory factors; accordingly, leptin may be involved in the process of articular inflammation (39). In another study conducted by Ku et al., it was shown that leptin concentration of intra-articular fluid is closely related to the severity of cartilage diseases in the radiographic image (35). Therefore, it is suggested that leptin concentration of intra-articular fluid is closely related to the severity of the cartilage disease in the radiographic image. Thus, it is suggested that leptin may be effective as a marker for quantitative assessment of osteoarthritis (35). According to the research conducted so far, we can say that leptin contributes in increasing intensity of osteoarthritis in addition to being implicated in the development of it. In addition, the fact that leptin gene expression of cartilage and the leptin level of the articular fluid is closely connected with the BMI, and leptin level in the articular fluid is higher than the serum level (32), suggests that leptin may be a link between obesity and osteoarthritis (40).

Role of adiponectin in the pathogenesis of knee osteoarthritis remains unclear to some extent so that it was known as a protective factor (43), but clinical observations have suggested an antagonistic role for it. Plasma adiponectin levels in 35 patients with osteoarthritis were significantly higher than healthy control subjects (44), and also, it was higher in women with erosive osteoarthritis of the hand compared to nonerosive osteoarthritis women (45). A study measured the adiponectin level in patients with OA and rheumatoid arthritis (RA), and found that it is in a higher level in the RA, and believes that the increased levels of adiponectin is an attempt to reduce the proinflammatory effect of leptin (46, 47). Furthermore, adiponectin levels in synovial fluid of 76 men with osteoarthritis were in direct contact with disease severity (48) and in 30 women, it was contact with knee osteoarthritis with aggrecan degradation (49). More laboratory studies support the devastating impact of adiponectin on osteoarthritis through leptin-like mechanisms (50-52). Although, at first glance, the results of our study suggest a negative relationship between adiponectin and osteoarthritis, distribution of adiponectin in the chart shows that the overall level of adiponectin in patients with osteoarthritis is still higher than the adiponectin level in the control group, despite the decrease in BMI, the idea that the adiponectin level has a destructive role is not farfetched (Figure 1).

The results of the current study showed that levels of hormones secreted from adipose tissue, in people with knee OA, were higher compared to the control group, indicating the possible effect of these hormones on the process of osteoarthritis. Finally, we showed that after adjusting for age, sex, BMI, leptin and adiponectin are significantly correlated with the amount of pain indicating higher levels of leptin and adiponectin lead to increased pain.

Footnote

Authors' Contribution: All authors had a significant contribution in study design, collecting data, writing the manuscript draft and critical revision of the manuscript.

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