Impact of Obesity on Activity and Severity Parameters of Osteoarthritis

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Abstract: Obesity is characterized by increased plasma leptin concentrations. It was found that the elevated plasma leptin concentrations in morbidly obese patients may enhance constitutive immunological stimuli, leading to increased concentrations of acute phase proteins and other inflammatory markers, characteristic for a chronic inflammatory state. The paradigm that obesity predisposes people to OA because of extra-mechanical loading only has been shifted to the paradigm that metabolic factors (adipokines) are also involved in the pathophysiology of OA and hand joints are an ideal target to investigate the role of adipokines since they are not weight-bearing joints. **Objective:** To assess the impact of obesity and serum leptin levels on OA severity and on functional outcomes. **Methods:** The study included 48 candidates who were classified into two groups: group I; included 36 patients with OA which further subdivided into two subgroups obese and non obese OA patients. Group II; included 12 healthy non obese individuals as a control group. All candidates were subjected to full history taking, thorough clinical examination and laboratory investigation. OA was assessed using standard functional and radiological scores. **Results:** The OA group in the present study showed significantly higher WOMAC index, WOMAC total score, VAS of pain, HFAS and K-L score of knee joint in obese OA compared to non obese. Also, obese OA patients had significantly higher serum leptin and CRP levels. OA patients showed a high significant correlation between serum leptin levels and WOMAC scores, VAS of pain and K-L score of knee joint. Patients with erosive OA showed significant difference as regard DIP joint pain but no significance was found in all other parameters. **Conclusion:** Obesity has not only mechanical effect but also has metabolic effect on the different joints of OA patients. Moreover obesity and elevated serum leptin have a significant effect on clinical symptoms and severity of knee OA patients and on activity only not severity of hand OA patients.

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1. Introduction:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and increased health problems [1]. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness [2]. Human obesity is characterized by increased plasma leptin concentrations. Leptin, the product of the Ob gene is considered to be involved in satiety regulation and obesity. Leptin is primarily expressed in adipose tissue [3]. It was hypothesized that leptin is involved in the induction of this enhanced inflammatory state in obese subjects. The studied relation between BMI, leptin and inflammatory markers revealed that, elevated plasma leptin concentrations in morbidly obese patients may enhance constitutive immunological stimuli, leading to increased concentrations of acute phase proteins and other inflammatory markers, characteristic for a chronic inflammatory state [4].

OA is the most common joint disorder with symptoms in the hands, knees, hips, back, and neck. It is unclear exactly how excess weight influences OA. Clearly, being overweight increases the load placed on the joints such as the knee, which increases stress and could possibly hasten the breakdown of cartilage [5, 6]. However, overweight has also been associated with higher rates of hand OA in some studies suggesting the involvement of a circulating systemic factor as well [7]. The paradigm that obesity predisposes people to OA because of extra-mechanical loading only has been shifted to the paradigm that metabolic factors (adipokines) are also involved in the pathophysiology of OA [8]. Hand joints are an ideal target to investigate the role of adipokines since they are not weight-bearing, bringing into question a metabolic, rather than a mechanical, explanation for the association between obesity and OA [9, 10]. showed that there was no difference in serum level of resistin between patients with and without erosive

hand OA. They investigated the relation between adiponectin and hand OA, where they showed that the mean serum level of adiponectin was higher in 48 women with, than in 27 women without, erosive hand OA.

The association between baseline serum levels of leptin, adiponectin and resistin and radiographic progression of hand OA was investigated over 6 years considering mainly joint space narrowing. The mean leptin level in patients with hand OA progression was slightly higher than in patients without progression, after adjustment for age, sex and BMI, leptin and resistin levels were not associated with progression and adiponectin showed protective effect against hand OA progression [11].

2. Methods

Study design and patient selection

This study was carried out in Minia University Hospital. All patients were recruited from Rheumatology Outpatient Clinic in the period from October, 2012 to June, 3013. It included 48 patients, who were divided into two groups:

First group: 36 Patients with established OA, fulfilling Arthritis Rheum 1986 OA classification criteria, with permission from ACR [12]. This group was further subdivided into two subgroups; obese patients (BMI ≥25) and non-obese with BMI less than 25.

Second group: 12 non-obese healthy candidates (BMI<25)

Ethical considerations:

The nature of the present study was explained to all patients. The laboratory and radiological procedures represent standard care and pose no ethical conflicts. A verbal consent was obtained from all patients.

Study parameters:

All patients were subjected to full history taking, thorough clinical examination, laboratory investigation. Radiological assessment, assessment of disease activity and severity in O.A patients by standard functional and radiological scores were performed.

Assessment of disease activity and severity

WOMAC score used to assess pain, stiffness, and physical function in patients with hip and / or knee OA [13]. Functional index for hand Osteoarthritis (FIHOA) to measure hand function in patients with hand osteoarthritis [14]. Kellgren-Lawrence grading scale of knee joints: for detect grading and assess severity of knee OA [15]. K-L grading scale for 30 hand joints (5 DIP, 4 PIP, 5 MCP, CMC1/TS): for detect grading and assess severity of hand OA [15].

Assays

Erythrocyte sedimentation rate (ESR) was done by Westergren method [16]. C-Reactive protein (CRP) was done by latex agglutination slide test for qualitative and semi-quantitative determination of CRP in non-diluted serum [17]. Rheumatoid Factor: by latex fixation test [18]. Lipid profile: Total cholesterol, triglycerides and high density cholesterol were measured. LDL-Cholesterol was calculated according to the equation LDL = Total cholesterol – HDL – (Triglycerides ÷ 5) [19]. Serum leptin was measured using the enzyme linked immunosrobent assay (ELISA)

Statistical analysis:

Data were coded, entered and analyzed by the statistical Package for the Social Sciences (SPSS for windows version 16.0). Two-tailed tests were used throughout and statistical significance was set at the conventional level of less than 0.05.

The following statistical tests were carried out:

I- Descriptive statistics: The range, means and standard deviation were calculated for interval and ordinary variables and frequencies and percentages for categorical variables.

II- Group comparisons: Comparisons were done by three procedures:

* Student's t-test: The t-test was used to compare the difference between two group means in interval and ordinal variables.

* The chi-squared (χ^2) test: The χ^2 is a nonparametric measure of the statistical independence of the categories of two variables measured on the nominal or dichotomous scale.

We used the χ^2 test to test the significance of the differences between the two and three groups in categorical variables.

*ANOVAs test: The analysis of variance (ANOVA test) is used to compare the difference between more than two group means in interval and ordinal variables.

III- Correlations: The Bivariate Correlations procedure computes Pearson's correlation coefficient with its significance levels. Pearson's correlation coefficient is a measure of linear association.

3. Result

Study population

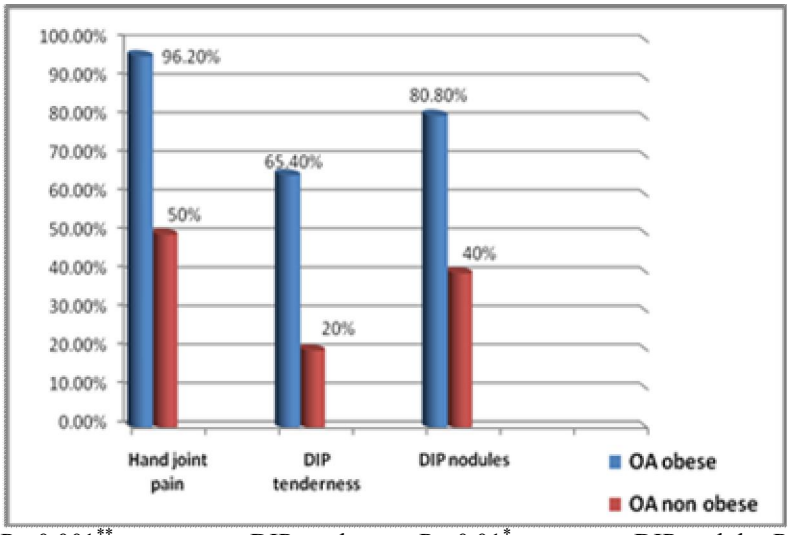
- **Group I**: included 36 OA patients, 31 females (86%) and 5 males (14%), their ages ranged from 45 - 68 years with a mean of 56.6 ± 5.9 years, and their disease duration ranged from 1-20 years with a mean of 5.35 ± 5.31 years.
- **Group II**: include 12 healthy individuals, 10 females (83.3%) and 2 males (16.7%), their age ranged from 22-41 years with a mean of 25.4± 5.6 years.

Clinical manifestations of OA patients.

All patients had knee pain, and crepitus, while 31 (86.1%) patients had knee joint tenderness, 10 (27.8%) had knee swelling and only 2 (5.6%) patients had knee deformity. Thirty patients (83.3%) had inactivity stiffness, and hand joints pain. Thirteen (36.1%) patients had 1st CMC pain, 11 (30.6%) patients had DIP pain, and 19 (52.8%) patients had DIP tenderness, while 25 (69.4%) patients had DIP nodules.

Clinical manifestations in OA subgroups.

Obese patients clearly had higher knee tenderness (p=0.0001), inactivity stiffness (p =0.01), hand joints pain (p =0.001), DIP joints tenderness (p =0.01) and DIP nodules (p =0.01). (fig 1).



Hand joint pain P= 0.001** DIP tenderness P= 0.01* DIP nodules P= 0.01*

Figure 1: Clinical manifestations of hand OA in subgroups

Table 1 shows the differences in activity and severity indices between obese and non-obese patients. There was a statistically high significant difference between obese and non obese patients as regard WOMAC index (p =0.0001), WOMAC total score (p =0.0001), VAS of pain (p =0.007) and FIHOA (p =0.04). (Table 1). Obese OA patients showed a significant higher K-L score of knee joint when compared to non-obese patients (p value= 0.0001), while there was no statistically significant difference was found as regard K-L score of hand joints.

Table 1: Differences in activity and severity indices between OA subgroups:

	OA obese N=26	OA non obese N=10	*T*	*p* value
WOMAC index (mean ± SD)	63.8 ± 9.6	42.6 ± 16.3	4.84	0.0001*
WOMAC total score (mean ± SD)	2.6 ± 0.39	1.7 ± 0.66	5.001	0.0001*
FIHOA (mean ± SD)	10.4 ± 0.81	6.0 ± 4.9	2.07	0.04*
VAS of pain (mean ± SD)	4.9 ± 1.4	3.5 ± 1.08	2.87	0.007*
K-L score of knee joint (mean ± SD)	2.8 ± 0.46	1.9 ± 0.31	5.9	0.0001**
K-L score of hand joint (mean ± SD)	53.9 ± 15.5	46.2 ± 15.1	1.2	0.23

By student's t-test *Statistical significant ($p < 0.05$)

WOMAC index: Western Ontario and McMaster Universities Osteoarthritis Index.

FIHOA: Functional index for hand Osteoarthritis.

VAS of pain: visual analogue scale of pain. K-L score: Kellgren-Lawrence (KL) score.

Obese OA subgroup showed a statistically higher level of TAG (p =0.008), serum cholesterol (p = 0.03), serum leptin (p =0.0001) and CRP (p =0.001) when compared to non-obese patients (Table 2).

Table 2: Differences in laboratory assessments between OA subgroups:

		OA obese N=26	OA non obese N=10	x^2/t	*P* value
Serum TAG	Range	56-223	49-92	2.79	0.008**
	Mean ± SD	122.1± 50.8	76 ± 15.4		
Serum CHOL	Range	80-309	61-252	2.25	0.03*
	Mean ± SD	159.4 ± 54.2	150.7 ± 50.7		
ESR 1st hr	Range	5-105	14-33	1.83	0.07
	Mean ± SD	35.8 ± 23.1	21.4 ± 5.2		
Serum Leptin	Range	4.6-53.6	0.15 – 4.6	14.01	0.0001**
	Median	23.5	5.5		
CRP	_	19 (73%)	1 (10%)	11.6	0.001**

Of the 35 patients with OA who were included in the study, 7 (20%) were classified as having erosive OA and 28 (80%) as having nonerosive OA. Comparing erosive and non erosive OA patients yields only significance in DIP joint pain.

Comparison between serum leptin in patients and controls.

Serum leptin showed a statistically significant higher level in OA patients when compared to control group (*p* value = 0.001).

Correlations between Obesity parameters and clinical manifestation in OA.

In OA, there was a high significant positive correlation between BMI and knee tenderness (*p* =0.002), inactivity stiffness (*p* =0.0001), and DIP tenderness (*p* =0.04). Also there was a significant positive correlation between WC and knee tenderness (0.01), inactivity stiffness (*p* =0.002), and DIP tenderness (0.007).

Correlations between Obesity parameters and laboratory finding in OA.

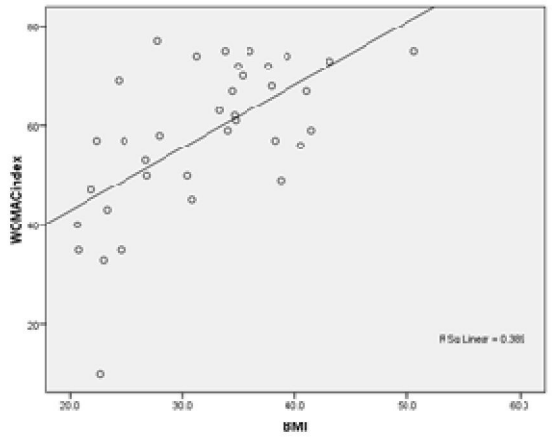
In OA, waist circumference (WC) showed significant positive correlation with TGA (*p* =0.004), serum leptin (*p* =0.0001) and CRP (*p* =0.0001). BMI showed a statistically significant positive correlation with ESR (*p* =0.04), serum leptin (*p* =0.0001) and CRP (*p* =0.0001).

Correlations between Obesity parameters and activity and severity indices in OA. There was a high significant correlation between obesity parameters (BMI & WC) on one hand and WOMAC index, WOMAC total score as well as K-L score of knee joint on the other hand (*p* =0.0001). VAS of pain was significantly positively correlated with BMI (*p* =0.0001) and with WC (*p* =0.002) (Table 3).

Table 3: Correlation between Obesity parameters and activity and severity indices in OA:

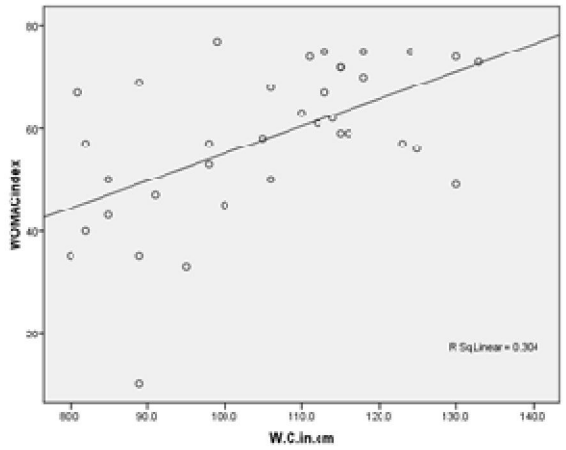
		BMI	WC
WOMAC index	R	0.62	0.55
	P value	0.0001**	0.0001*
WOMAC total score	R	0.63	0.56
	P value	0.0001**	0.0001*
HFAS	R	0.29	0.22
	P value	0.08	0.19
VAS of pain	R	0.55	0.49
	P value	0.0001**	0.002*
K-L score of knee joint	R	0.78	0.64
	P value	0.0001**	0.0001*
K-L score of hand joint	R	0.21	0.12
	P value	0.21	0.47

Using Pearson correlation; *Statistical significant ($p < 0.05$)



R= 0.62; P= 0.0001

Figure 2: correlation between BMI &WOMAC index in OA patients.



R= 0.55; P= 0.0001

Figure 3: correlation between WC &WOMAC index in OA patients.

Correlations between serum Leptin and other laboratory and clinical findings in OA.

There was a highly significant positive correlation between serum leptin and both inactivity stiffness (p =0.0001) and DIP tenderness (p =0.0001).

There was a high significant positive correlation between serum leptin and CRP (p =0.003).

Serum leptin was also significantly correlated with WOMAC index (p =0.01) and K-L score of knee joint (p =0.004).

Finally, a linear regression analysis was carried out to identify the most significant risk factors affecting serum leptin. It was noticed that: the BMI was the first and most significant risk factor (β=0.83; p =0,004), followed by WOMAC total score, WOMAC index, CRP, WC in cm, KL scale of knee joint, serum TAG, serum CHOL and VAS of pain, respectively. (Table 4)

Table 4: Risk factors affecting serum leptin in O.A:

Variables	Beta	*P* value
BMI	0.83	0.004
WOMAC total score	0.58	0.7
WOMAC index	-0.57	0.7
CRP	-0.50	0.07
WC in cm	0.36	0.1
KL scale of knee joint	0.039	0.8
Serum TAG	0.039	0.8
Serum CHOL	0.038	0.7
VAS of pain	-0.034	0.8

Dependant variable is serum leptin

4. Discussion

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and increased health problems [1].

Cicuttini *et al.* (1996) found that the paradigm that obesity predisposes people to OA because of extra-mechanical loading only has shifted to the paradigm that metabolic factors (adipokines) are also involved in the pathophysiology of OA [8].

In the current study, obese OA patients had more knee tenderness, inactivity stiffness, hand joints pain, DIP tenderness and DIP nodules compared to non obese ones. Also, obese OA patients when compared to non-obese ones in terms of activity and severity indices; they had higher WOMAC index, WOMAC total score, VAS of pain, and K-L score of knee joint. This was in agreement with the findings of Jarvenpaa *et al.* (2012), who studied 48 patients with knee OA grade IV. They were divided in two groups according their BMI; into obese and non obese and found that the obese patients had poorer clinical and functional scores where their WOMAC scores were significantly higher compared to non-obese as regard pain, stiffness and physical function. Differences were also found in clinical success at the final follow-up after total knee arthroplasty (TKA) and non-obese patients reached better percentage improvement in the functional scores compared to obese patients [20].

Obese OA patients had higher serum leptin and CRP compared to non obese ones. Similarly, Turki *et al.* (2009), studied 30 OA patients and found that the mean serum leptin level, serum TAG and serum CHOL were significantly higher in obese than non-obese patients [21].

Obesity parameters were significantly correlated with clinical manifestations, activity and severity indices. These were similar to Christensen et al., (2007), who also found that obese OA individuals had higher pain scores and more disability compared to their own scores after weight reduction [22].

Obesity parameters show a significant correlation with acute phase reactants in patients and serum leptin was correlated with CRP levels, this in agreement with, van Dielen et al., (2001), who found that plasma leptin concentrations correlated strongly with BMI and CRP with marked increase in morbidly obese subjects[23].

The present study also shows a high significant correlation between serum leptin and activity and severity of knee OA as regard WOMAC scores, VAS of pain and K-L score of knee joint. This was in agreement with, Miller et al., (2004), who carried out a research on overweight and obese adults with symptomatic knee OA and measured the serum leptin and assessed it's relation to self-reported difficulty in performing selected physical activities, they found a significant correlation between the elevated serum leptin and the poorer self-reported physical function [24].

In contrary to these findings, Iwamoto *et al.* (2011), in a study done on postmenopausal Japanese women with OA of the knee, it was found that there is no significant correlation between the serum leptin concentration and the radiographic grade of knee OA. This may be due to the different management protocols and inclusion criteria. As most of the patients in their study were receiving weekly to monthly intraarticular injections of hyaluronate sodium and/or oral NSAIDs but the patients in the presented study were receiving NSAIDS only also they didn't consider BMI as a parameter [25].

Erosive hand OA patients didn't show significant difference in functional, laboratory and radiolological scores as well as obesity parameters and this was consistent with Filková *et al.* 2009 and Yusuf *et al.* 2011 who found no difference in serum leptin in patients with erosive hand OA or with progression of hand OA respectively

The RA group in the presented study showed a significant differences in activity indices in terms of HAQ index, DAS 28, VAS of pain and AI and in inflammatory markers as ESR 1st hr, CRP and RF [10, 11].

In the present study, leptin showed a statistically higher level in OA patients when compared to the level in control group. This was in agreement with De Boer et al., 2012, who reported a higher serum leptin in OA patients when compared to control and was significantly associated with high BMI [26].

Conclusion

It was concluded that obesity has not only mechanical effect but also has metabolic effect on the different joints of OA patients. Obesity and elevated serum leptin have a significant effect on clinical symptoms, activity and severity of knee OA patients and on activity only not severity of hand OA patients.

Further studies are recommended to be done on large number of patients with long term follow up to show significance use of weight loss regimens as one of the line management in OA patients.

Further studies required for erosive subtype of OA to be done on larger numbers to determine its relation to obesity and determine its laboratory profile.

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