A STUDY OF LEPTIN & LIPID PROFILE IN A SAMPLE OF IRAQI PATIENTS WITH KNEE OSTEOARTHRITIS.

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Summary

Background: New data suggests that joint damage in Knee Osteoarthritis (KOA) may be caused by systemic factors like adipose tissue products; Adipokines, which may provide a metabolic link between obesity & KOA. Recently, one of the known adipokines named LEPTIN has been linked to KOA because it can be detected in serum & synovial fluid of patients with KOA.

Objective: To evaluate the contribution of Leptin & serum lipids to the pathophysiology of Osteoarthritis in Iraqi patients with Knee OA.

Subjects& Methods: The study was carried on 90 subjects divided into four groups:
Knee Osteoarthritis cases group (n=60).
Control group (n=30).
Obese subjects group (n=60).
Non-obese subjects group (n=30).

KOA cases were diagnosed clinically whereas obesity was specified by BMI ≥25kg/m2. For all subjects studied measurements of fasting serum leptin and lipid profile have been done.

Results: Mean serum leptin level was significantly higher in KOA cases compared to control group (P<0.001), and higher in obese than non-obese subjects (P<0.001). Serum leptin level also showed a strong positive correlation with BMI (r=0.501, P<0.01).

Conclusions: Leptin may play an important role in the pathogenesis of KOA. In addition abnormal lipid profile and obesity are important risk factors for KOA.

Keywords: Knee Osteoarthritis, Obesity, Leptin.

Introduction :

Osteoarthritis

It is a chronic degenerative disorder characterized by gradual loss of articular cartilage, combined with thickening of the subchondral bone, bony outgrowths (osteophytes) at the joint margins, and mild, chronic nonspecific synovial inflammation [1].

Although the etiology of OA is not established, the main risk factors are well known and commonly include mechanical, biochemical and genetic factors. Of these risk factors, obesity is beyond doubt a prominent one because of the increased weight bearing on joints, altered biomechanics, genetic predisposition & altered metabolism associated with obesity.[2]

Obesity and osteoarthritis are two commonly encountered problems that can lead to a significant physical and emotional disability. Since obesity is the single most important modifiable risk factor for OA, improved understanding of its contribution to pathogenesis of OA will hopefully lead to improved treatment and subsequent amelioration of this important risk factor for OA [3].

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Obesity

It is the commonest nutritional disorder in affluent societies [4]. Obesity has become a leading health concern because this condition is a chronic, complex, multifactorial disease in which a person's weight is ≥20% of the ideal weight for a given height [5].

Although not a direct measure of obesity, the most widely used method to gauge obesity is the Body Mass Index (BMI), which is equal to weight/Height^2 in (kilogram/meter^2). A major regulator body weight is the adipocyte-derived hormone Leptin, which acts through the hypothalamus to influence appetite, energy expenditure and neuroendocrine functions[6,7].

There is increased interest in the concept of a body weight "set point." This idea is supported by physiologic mechanisms centered around a sensing system in adipose tissue that reflects fat stores and a receptor, or "adipostat," that is in the hypothalamic centers. The recent discovery of the ***ob*** gene, and its product leptin, provides a molecular basis for this physiologic concept [6].

Leptin

It is a 16 kDa adipocyte-secreted hormone that regulates weight centrally and links nutritional status with neuroendocrine and immune function [8].

Its name is derived from the Greek root *Leptos*, meaning thin. The vast majorities of obese people have increased leptin levels but do not have mutations of either leptin or its receptor**.** They appear, therefore, to have a form of functional "leptin resistance" [6].

However, the initial view of leptin as a simple hormone has been superseded by an appreciation of its more complex effects in energy balance and recognition of its involvement in the control of neuro-endocrine factors, immunity and development [7].

Leptin & Osteoarthritis

The current working hypothesis is that adipokines, cytokines & other factors produced and released by White Adipose Tissue (WAT) are responsible for a chronic subclinical pro-inflammatory state. Changes in levels of systemic adipokines, local adipokines or both have been reported in this inflammatory condition, with most studies focusing on leptin [9].

Leptin levels are elevated in synovial fluid of KOA patients and correlate with BMI. Leptin and its receptor are also expressed in osteoarthritic chondrocytes [10], and it induces production of pro-inflammatory cytokines in human synovial fibroblasts [11].

Osteophytes, which are osteocartilagenous metaplastic tissues, represent the major source of leptin in osteoarthritic synovial joints [2]. Interestingly, the pattern and level of leptin expression are related to grade of cartilage destruction [12].

SUBJECTS AND METHODS

Subjects:

This study was conducted in Medical City, Baghdad Teaching Hospital (Rheumatology& Rehabilitation Consultation Department), and Teaching Laboratories during the period from June 2007 to December 2007.

A total number of 90 subjects included in the study were divided according to presence of KOA and/or Obesity into four groups:

1. Knee Osteoarthritis cases group (n=60).
2. Control group (n=30).
3. Obese subjects group (n=60).
4. Non-obese subjects group (n=30).

KOA cases were diagnosed clinically and radiologically, whereas obesity was specified by BMI $\geq$25kg/m^2.

Methods:

The following biochemical tests were done for all study subjects:

1. Measurement of Leptin in serum using the Leptin (sandwich) Enzyme immunoassay kit. This assay is intended for *in vitro* diagnostic use only. It is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle.
2. Lipid profile assessment using Kits from SPINREACT-CЄ to measure Triglycerides (TG), Total Cholesterol (TC), Low Density Lipoprotein (LDL) & High Density Lipoprotein (HDL) levels in serum.

Statistical analysis

All data were arranged and tabulated in number and percentage. To compare the significance of the difference in the mean values of any two groups chosen, student t-test was applied; P<0.05 was considered statistically significant. The correlation coefficient (r) test is used to describe the association between the different studied parameters; P<0.05 was considered statistically significant.

RESULTS

Statistical analysis of KOA Cases group:

There was no significant difference in mean age, TG, LDL and total cholesterol levels between obese cases and non-obese cases, P>0.05.

Leptin level in obese cases was significantly elevated compared to non-obese cases, P<0.001. (Figure1). Mean BMI was higher in obese cases than non-obese cases, P<0.001. Mean HDL was lower in obese cases than non-obese cases, P<0.05. (Table1).

Table (1): Statistical Data of KOA Cases

Characteristics	Obese	Non-obese	P value
1. **Number - %**	40 – 66.7%	20 – 33.3%	-
2. **Age (years)**	53.88±6.9	52.55±6.8	NS
3. **TG (mg/dl)**	145.75±61	130.05±47.9	NS
4. **Cholesterol(mg/dl)**	209.88±30.97	218.75±23.83	NS
5. **HDL (mg/dl)**	37.35±8.14	44.90±9.41	<0.05
6. **LDL (mg/dl)**	146.78±30.68	153.45±30.93	NS
7. **BMI (kg/m^2)**	33.26±4.32	22.62±2.55	<0.001
8. **Leptin (ng/ml)**	23.60±4.53	15.77±1.32	<0.001

Statistical analysis of Obese group:

There was no significant difference in mean age, TG, LDL, total cholesterol levels and BMI between obese cases and obese controls, P>0.05.

Mean serum leptin was significantly lower in obese controls compared to obese cases, P<0.001. (Figure1). Mean HDL was lower in obese cases than obese controls, P<0.05. (Table 2).

Table (2): Statistical Data of Obese Group

Characteristics	Case	Control	P value
1. **Number - %**	40 – 66.7%	20 – 66.7%	-
2. **Age (years)**	53.88±6.91	52.10±7.21	NS
3. **TG (mg/dl)**	145.75±61	126±29.62	NS
4. **Cholesterol(mg/dl)**	209.88±30.97	208.75±23.16	NS
5. **HDL (mg/dl)**	37.35±8.14	42.85±8.22	<0.05
6. **LDL (mg/dl)**	146.78±30.68	141.20±22.69	NS
7. **BMI (kg/m^2)**	33.26±4.32	34.94±4.24	NS
8. **Leptin (ng/ml)**	23.60±4.53	14.53±1.89	<0.001

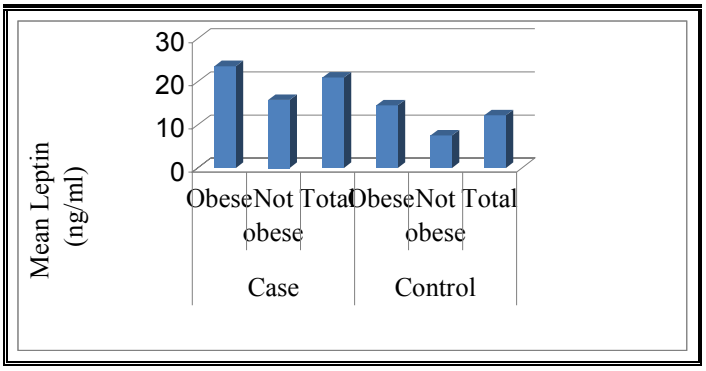

Figure (1): Mean values of serum Leptin in study subjects

Correlations

This study showed that serum leptin correlates positively & strongly with BMI [r=0.501, p<0.01]. (Figure 2). It showed also that serum HDL correlates negatively & strongly with serum TG [r=-0.775, p<0.01], and a strong positive correlation was found between total cholesterol and LDL [r=0.809, p<0.01].

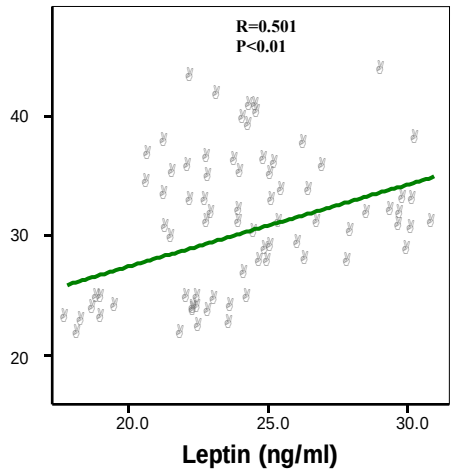

Figure (2): Correlation between Serum Leptin and BMI

DISCUSSION

It is increasingly evident that adipose tissue secrets a large variety of highly active proteins including cytokines, chemokines, and hormone like factors, such as leptin which is increased in obese subjects and is closely related to fat mass and BMI and declines with weight loss [9].

In this study it was found that mean serum leptin level was higher in obese group than non-obese group and serum leptin was positively& strongly correlated with BMI which is an important index of obesity. Similar findings were reported by previous studies [13,14].

Circulating leptin levels appear to be one of the best biological markers of obesity& hyperleptinemia is closely associated with several risk factors related to obesity syndrome [15].

The recent studies on KOA have focused more on evaluation of biochemical markers in serum and/or synovial fluid of knee joint; such as, adipokines, MMPs, TIMPs, toxic oxygen radicals, and others [2,10,11,16]. On the other hand, very few studies have assessed the relation between the structural severity of KOA and biochemical markers levels [17,18].

In the present study patients with KOA had a significantly higher level of leptin when compared to control group, this is in agreement with previous studies [2,10,11,19,20]. Adipose tissue in the joint may act locally to influence joint metabolism. Leptin is an example of molecules that may act systemically and/or locally to influence joint tissue [19].

The increased expression of leptin in markedly damaged cartilage suggests that leptin may trigger cartilage destruction in KOA, especially when associated with some local factors [20]. The mechanical loading on knee joint causes physical perturbations of chondrocytes that are transduced into metabolic responses represented by growth factors, MMPs, cytokines and adipokines. These constitute the normal mechanobiology of the chondrocyte [21].

The elucidation of the exact role of biochemical factors that regulate the behavior of the chondrocytes and other cells in the joint will lead to identification of new targets for osteoarthritis therapy [22].

Many Iraqi studies have discussed the relationship between leptin and other chemical parameters or some clinical conditions; such as, its relation to Inhibin level in infertile women [23], with aging and Growth Hormone level [24], and to Type-2 Diabetes Mellitus in postmenopausal women [25].

To the best of our knowledge, the present research is the first to study the level of serum leptin in Iraqi patients with KOA.

CONCLUSIONS

Leptin may play an important role in the pathogenesis of KOA. Also abnormal lipid profile and obesity are important risk factors for KOA; thus, therapeutic measures like weight reduction and control of serum lipid concentrations in obese patients may be beneficial in protection against KOA.

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