Study the levels of Leptin, and Adiponectin with Paraoxonase in Obese Individuals (male & female)

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Abstract

Obesity is a well-known risk factor of metabolic complications and cardiovascular disease. Associations between anthropometric measurements and fat distribution and risk factors for cardiovascular disease have been demonstrated in several populations.

To study the association of various measures of body mass index (BMI), waist circumference (WC), percentage of body fat (%BF), with leptin, Adiponectin, and paraoxonase. To study the association between leptin , adiponectin with Paraoxonase.

This study conducted from of February 2013 until March 2014, all individuals were randomly recruited from Kirkuk and Tikrit Governorate .Hormonal assay of leptin, adiponectin, Paraoxonase, and glucose. Blood samples collected from 220 individuals, and these samples were divided into three groups according to BMI. Group 1 (Normal Weight group n=80), Group 2 (Over Weight group, n=58), Group 3 (Obese group, n=62) .

The statistical analysis (students t-test) exhibited significant ($P \leq 0.0001$)elevation for leptin , paraoxonase, and glucose, while significant decrease in adiponectin in over weight and obese groups compared with normal weight groups.

The correlation coefficient (r) between Leptin and other parameters were calculated with regression plot showed a negative correlation with adiponectin, and paraoxonase in over weight and obese group. There was a positive correlation between adiponectin with paraoxonase, but a negative correlation with leptin, in over weight and obese group.

Conclusion: Adiponectin as hormone play an important role in the prevention of hyperlipidemia, and consequently atherosclerosis and its complications while Leptin act as atherosclerotic factors. The results indicated that adiponectin positively associated with paraoxonase while Leptin negatively correlated with paraoxonase.

Key word: Obesity, Leptin, and Adiponectin , Paraoxonase

Introduction

In recent decades, the prevalence of obesity has increased alarmingly, making it a significant health problem in not only high-income countries, but low and middle-income countries as well [(1)]. Obesity is defined as abnormal or excessive fat accumulation that presents a risk to human health [(2)]**.** The current obesity plague is stimulated by the accessibility to high caloric food along with performing less physical activity[(3,4)]**.**

Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. It does not only respond to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine functions. These factors include leptin, adiponectin, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, acylation stimulating protein and resistin[(5)]**.**

Leptin, (from the Greek word leptos, meaning thin) is a peptide hormone, secreted from adipose tissue, which influences energy homeostasis, immune and neuroendocrine function[(6)]**.**In humans, it is well established that plasma leptin levels are directly proportional to percentage body fat. Most obese individuals have high concentrations of leptin in their serum and blood plasma but exhibit leptin resistance because of decreased leptin transport into the central nervous system or downregulation of leptin receptors[(6)]**.**

The Paraoxonase (PON, aryldialkyl phosphatase, E.C. 3.1.8.1), is an Ca- dependent enzyme that is synthesized in liver. It is related to HDL-C and has 43-45 KDa molecular weight with glycoprotein structure. Paraoxonase refers to a family of enzymes that includes three members in mammals, namely, PON1, PON2, and PON3[(7)].

Materials and Methods

Our study was conducted in Tikrit Teaching Hospital in Tikrit province during the period from February 2013 until March 2014,

among 120 obese healthy subjects (mean age 51.4 ±11.4 years; 84 women and 36 men) For the comparison, a total of 80 apparently healthy control subjects (mean age 41.2 ± 6.3 years; 45 women and 35 men) Subjects were divided into three categories according to BMI [(8)].:

1. Normal Weight group: BMI 18.5 - 24.9 kg/m^2 (n=80)..
2. Over Weight group: BMIs 25.0 - 29.9 kg/m^2 (n=58).
3. Obese group : BMIs $\geq$ 30 kg/m^2 (n=62).

Anthropometric Measurements:

Body mass index was calculated as weight in kilograms divided by the square of height in meters. BMI= weight (kg)/height (m)^2.Waist circumference was measured in centimeters (cm) at the end of normal expiration half way between the lowest rib and the iliac crest with the investigator standing at the

side to ensure that the measuring tape is horizontal across the back and the front of the participant [9].

Body fat can be estimated from a person's BMI by the following formula: Body Fat% = (1.2 x BMI) + (0.23 x age) − 5.4 − (10.8 x gender).Where gender is equal to 0 if female and to 1 if male[10].

Biochemical Test:

For each participant, fasting blood samples were collected into the non-heparinized blood in the plain tubes were left to clot and then centrifuged at 4000 rpm for 10 minutes to separate the serum and stored at -20 C° until assayed. Leptin and adiponectin, were determinated using 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[11]. Paraoxonase activity assay was performed using paraoxon (O,O-diethyl-O-p-nitrophenyl phosphate; Sigma-Aldrich ,Germany) as a substrate according to the method described by [12].

Statistical analysis:

Statistical analysis was performed by statisticians with the SPSS 15.01 Statistical Package for Social Sciences and also Excel 2003. Data analysis was done using chi-square test for tables with frequencies, while independent sample t-test was used for tables with means and standard Deviation. P value of ≤ 0.01was used as the level of significance. Correlation coefficient used to find the correlation between studied markers by using Pearson correlation.

Results

Demographic Distribution of Study population:-

In the present study, adiponectin, lipid Profile tests were measured for 200 individuals (80 control and 120 obese individuals) divided into three groups as summarized in table (1).

Table(1) Characteristics distribution of Study Population.

Groups	Normal weight	Over weight	Obese	Total
Male	35	12	24	71
Female	45	46	38	129
Total	80	58	62	200

Anthropometrics parameters:

Value of BMI, waist circumference, and BF were compared between the studied groups and control groups using analysis of variance t-test of significant as in table (2-4).

Table(2): Comparison Between weight Groups and BMI (Kg/m^2).

Weight groups	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	21.388 ± 1.779c	21.090 ± 1.684c	21.620 ± 1.835c
Overweight	26.560 ± 1.567b	27.185 ± 1.661b	26.410 ± 1.525b
Obese	34.572 ± 3.212a	35.350 ± 2.530a	34.080 ± 3.520a
P	0. 01	0.01	0.01

Table(3):Comparison Between weight Groups and Waist Circumference (CM).

Weight groups	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	74.15 ± 5.74c	78.20 ± 4.38c	71.000 ± 4.596c
Overweight	92.47 ± 4.00b	95.00 ± 5.20b	91.870 ± 3.463b
Obese	102.64 ± 8.59a	110.83 ± 6.51a	97.460 ± 4.935a
P	0.01	0.01	0.01

Table(4): Comparison Between weight Groups and Body Fat (%).

Weight groups	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	26.017 ± 1.404c	25.890 ± 1.557c	26.115 ± 1.283c
Overweight	31.856 ± 2.736b	32.177 ± 2.682b	31.779 ± 2.772b
Obese	37.503 ± 2.490a	37.792 ± 2.761a	37.320 ± 2.322a
P	0.01	0.01	0.01

Biochemical markers

Serum levels of glucose, leptin adiponectin and paraoxonase were compared between the patients groups and controls groups using analysis of variance t-test of significant as in table (3-3).

Table(5): Comparison Between weight Groups and Leptin (ng/ml).

Weight group	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	6.91 ± 2.96c	6.618 ± 2.241c	7.13 ± 3.43c
Overweight	28.42 ± 5.07b	26.457 ± 2.600b	28.89 ± 5.42b
Obese	37.01 ± 26.55a	34.319 ± 5.126a	38.71 ± 33.74a
P	0. 01	0. 01	0. 01

Table(6): Comparison Between weight Groups and Adiponectin (µg/ml).

Weight groups	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	8.156 ± 1.424a	7.970 ± 1.048a	8.300 ± 1.656a
Overweight	5.016 ± 2.236b	5.924 ± 1.964b	4.794 ± 2.262b
Obese	3.145 ± 1.287c	2.790 ± 1.143c	3.370 ± 1.337c
P	0.01	0.01	0.01

Table(7): Comparison Between weight Groups and Paraoxonase (U/L).

Weight Groups	Total Mean ± SD	Males Mean ± SD	Females Mean ± SD
Normal weight	156.79 ± 11.75a	145.40 ± 5.14a	165.65 ± 6.64a
Overweight	130.79 ± 5.56b	140.80 ± 2.98b	128.40 ± 2.49b
Obese	121.03 ± 8.20c	112.80 ± 5.25c	126.23 ± 4.69b
P	0.01	0.01	0.01

Correlation

Our study shows that serum leptin correlates negatively with adiponectin in over weight group (r=-0.167), in obese group (r=-0.165) and with paraoxonase in over weight group (r=-0.205), in obese group (r=-0.189) but correlates positively with BMI (r=0.124) in over weight group, in obese group (r=0.156).Serum adiponectin correlates positively with paraoxonase in over weight group (r=0.171), in obese group (r=0.321), but correlates negatively with BMI (r=-0.133) over weight group, in obese group (r=-0.108).The negative correlation was found between paraoxonase with BMI in over weight group (r=-0.119) , in obese group (r=-0.128), also with waist circumference in over weight (r=-0.544), and obese group (r=-0.612) also with body Fat over weight group (r=-0.184), in obese group (r= -0.190).

Discussion

The mean serum leptin concentration in obese humans is approximately 40 ng/mL, as compared with 4 ng/mL in the normal-weight individuals. An increase in plasma leptin suggests that obesity is the result of resistance to leptin. A low or normal plasma concentration of leptin in the context of obesity suggests decreased production of leptin[13].

As previous studies have reported, leptin levels were higher in obese individuals than in normal-weight individuals[13,14]. Regardless of weight, leptin seems to correlate better with subcutaneous fat rather than with visceral fat in both obese and non-obese subjects .This may be due to a diminished response in the leptin receptor signaling pathway, poor penetration of the blood-brain barrier by leptin, or due to the presence of a less active molecular forms of leptin In addition, the deficient leptin in nonobese subjects as compared to obese subjects is likely to be a target for leptin therapy, whereas obese subject with high leptin levels is likely to be resistant to leptin therapy . Leptin resistance may occur directly as a result of obesity, but these may also be a lack of sensitivity to circulating leptin which could contribute to the etiology of obesity [6].

The mechanism of leptin resistance in obesity is not yet identified. Data from studies of animals indicate that many factors may influence the activity of the neural circuit that regulates body weight. The entry of leptin into cerebrospinal fluid through the OB-Ra receptor may be limiting; morbid obesity could result when the plasma leptin levels exceed the capacity of the transport system. Factors that directly modulate energy expenditure or activate adipogenesis and

lipogenesis could also result in apparent leptin resistance [13].

Our results have also shown that there was a gender difference in the correlation between serum leptin and BMI in male and female participants as in table (5).

Previous studies have shown gender differences in adipokines concentrations[15,16]. Ursula and Axel. [17], which are probably the result of gender-specific hormonal differences between males and females, with an extremely important role of estrogen and different BF distribution. Females have a higher percentage of body fat than males and men are at greater risk of CHD than women per unit of circulating leptin increase, and males have also a larger intra-abdominal (visceral) fat mass. After menopause, there is a redistribution of fat depots, and post-menopausal females develop increased amounts of visceral fat[18].

Other studies showed that the increase in leptin concentration with age was associated with a decrease in the concentration of soluble leptin receptor, and age related changes in the concentrations of both leptin and its soluble receptor preceded the pubertal increase in gonadal hormones[17]. In the present study, there is a correlation between leptin concentration and the WC that is positive This is due to the close relation between BMI, WC and body fat content in addition to the responsibility of visceral and subcutaneous fat for producing leptin [6]. which is in compliance with other recent study[19].

previous studies in Japanese individuals demonstrated plasma adiponectin concentration was negatively correlated with BMI and hence lower in obese, than in lean subjects; our results, in agreement with this finding, demonstrated that plasma adiponectin concentrations are inversely related to BMI and WC. Therefore, our results also confirm that adiponectin is the only adipose-specific protein known to date, that, despite its exclusive production in white adipose tissue, is negatively correlated with obesity, findings similar to those in rodents where the murine homologue of adiponectin-adipo Q is also downregulated in obesity. The adiponectin gene is predominantly expressed in AT and its expression decreases in obese diabetic (db/db) murrain models [20,21].There were no significant differences between males and females Regarding adiponectin , our finding was consistent with two other reports that failed to observe the sex difference [22-24].

In contrast, some reports revealed that women had significantly higher serum adiponectin levels than men of the same BMI . The suggested reason was that women had more body fat percentage which reflects the higher adiponectin expression[25,26].

Some reports suggested that sexual hormones regulate the production of adiponectin, although it is controversial how these hormones, such as estrogen and testosterone , are involved in the regulation of plasma adiponectin level[27-28]. pointed out that androgens might inhibit the production of adiponectin and that might induce a gender difference[20-29]. showed that both testosterone and estrogen inhibited adiponectin, but the regulation by estrogen was weak and the regulation by testosterone was strong[21] .

The results showed that there was negative correlation between adiponectin, and leptin , this relationship may be due to fact that all these hormones are from same source (the adipose tissue) and this may make us to think if there was a negative axis on production or on gene expression on each other, this relationship need more investigation and study. Although adiponectin is secreted mainly from AT, its levels are paradoxically lower in obese than in lean humans which is in contrast to most other adipocytokines, whose levels are increased in obesity in proportion to increasing total body fat mass. It is possible that although adiponectin expression is activated during adipogenesis, a feedback inhibition in its production may occur during development of fat mass due to increase in the production of other adipocytokines. In addition, adipocytokines such as TNF-α may decrease adipocyte expression and secretion of adiponectin[21].

Results of other studies supported an inverse correlation between serum adiponectin and serum leptin levels[30]. indicated that adiponectin, contrary to leptin, was negatively correlated with fasting plasma glucose, TC/HDL-C ratio and TG, whereas it was positively correlated with HDL-C[30-31]. reported that decreased serum adiponectin and increased leptin levels are found in subjects with familial combined hyperlipidemia characterized by increased levels of total cholesterol, TG and/or apolipoprotein B[31].

Currently, only a few studies examined the correlation between obesity and PON1.HDL-PON is a calcium-dependent esterase that can hydrolyze oxidized phospholipids, thereby protecting lipoprotein (LDL, HDL) and membrane from oxidative changes. The enzymatic activity of HDL-PON varies greatly among healthy people, and individuals with low PON activity are at greater risk for developing diseases involving OS and LPO [32].Ferretti *et al*. demonstrated that there is increased oxidation of LDL-C and HDL-C, and low levels of Paraoxonase activity in obese subjects compared with healthy individuals[33].The protective role of PON in obesity is also supported by an observed increase in paraoxonase activity and a decrease in BMI in obese patients who were prescribed orlistat (a drug designed to treat obesity) in addition to a reduced-calorie diet[34-35].

described lower serum PON activity in patients with reduced body weight[35].Another study reported that there are changes in the activity of PON in overweight and obese women after a reduced-calorie dietary plan, which is reflected in a reduction in BMI and a significant reduction in LDL-C levels [36].In contrast, Tabur *et al.* found no change in PON activity in obesity and non-diabetic metabolic

syndrome, although OS and the inflammatory process were affected[37].

Paraoxonase can destroy active lipids in mildly oxidized LDL. Most serum PON1 is bound to the surface of HDL [38].Sorenson *et al*. demonstrated that PON1 is a lipid dependent enzyme; in fact, the conformation of PON1 within the hydrophobic environment of HDL is crucial for its activity. Phospholipids, especially those with long fatty acid chains, stabilize PON1 enzyme and are required to bind PON1 to lipoprotein surface [39].

The present study found that there is a negative relationship between paraoxonase and leptin. There are several mechanisms of adipokines influencing PON1 activity. Beltowki found that rats treated with leptin had decreased PON1 activity. These mechanisms may be the following : Leptin as a hydrophobic peptide can bind to HDL and inhibit directly the PON1 enzyme. On the other hand, leptin enhances oxidative inflammatory cytokines and other acute phase proteins which have diminishing effect on hepatic[40].

Paraoxonase through the enhancement of the acute phase response. Leptin also enhance the of serum amyloid A protein which can replace apoA-I in HDL. ApoA-1 plays a major role in stabilizing the structure of PON1. Leptin may have modulatory effect through the alteration of the lipid content in HDL particles; inverse correlation have been observed between leptin, HDL, and apo A-1 in human subjects [41].

The present study found that there is a positive relationship between paraoxonase and adiponectin. Adiponectin is an independent variable of serum PON1, which may contribute to the anti-atherosclerotic effect of adiponectin. BMI is an independent predictor of PON1 activity(42).Maria Fernanda reported that oxLDL can be internalized by the adipocyte, which contributes to its proliferation by increasing the AT mass . Hence, we hypothesized that PON1 polymorphisms with low antioxidant capacity may be associated with obese subjects[43].

Another explanation could be the decrease in the apoprotein content of HDL, which leads to an altered binding affinity and stability of PON1 [44].Due to the obese condition (in fact, due to the large quantities of leptin, proportional to the body fat mass), apoA1 gene, essential for PON1 transfer from hepatocytes to HDL and especially for PON1 activity [45], acquires mutations. On the other hand, adipocytes secretion profile, consisting of numerous biologically active peptides, might change [46].Adipokine imbalance leads to an increase of inflammatory mediators, which, in turn, will trigger the proatherogenic and proinflammatory activities of the HDL-PON1 complex [46].

Conclusion

Circulating leptin and hypoadiponectinemia levels appear to be one of the best biological markers of obesity, therefore hyperleptinemia and hypoadiponectinemia are closely associated with several risk factors related to obesity syndrome. Adiponectin as hormone play an important role in the prevention of hyperlipidemia, and consequently atherosclerosis and its complications while Leptin act as atherosclerotic factors .The results indicated that adiponectin positively associated with paraoxonase while Leptin negatively correlated with paraoxonase.

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دراسة مستويات اللبتين، الأديبونكتين وإنزيم الباروكسينيز في الأشخاص البدينين

انتظار رفعت سرحت

كلية الطب الاسنان ، جامعة تكريت ، تكريت ، العراق

الملخص

تعد السمنة احدى عوامل الخطورة للمضاعفات الاستقلابية والامراض القلبية – الوعائية, وقد تم ايضاح الروابط بين القياسات البشرية وتوزيع الدهون في الجسم ,والاختطار القلبي الوعائي في عدة مجموعات سكانية.

هدفت هذه الدراسة الى اختبار الارتباط بين عدة قياسات للسمنة, متضمنة السمنة الكلية للجسم (مؤشر كتلة الجسم, ونسبة الدهون في الجسم, ومحيط الخصر) مع هرمونات اللبتين, الأديبونكتين, إنزيم الباروكسينيز , في الأشخاص البدينة ومقارنتها مع الاشخاص ذوي الوزن الطبيعي. ودراسة العلاقة بين اللبتين, الأديبونكتين مع إنزيم الباروكسينيز .

اعتمدت هذه الدراسة على جمع عينات مصل الدم من 220 شخصاً, خلال الفترة من شباط 2013 الى اذار 2014 ,الاشخاص جندوا بشكل عشوائي من محافظة كركوك وتكريت, حيث خضع جميع هؤلاء الاشخاص في هذه الدراسة الى فحوصات هرمونات اللبتين , الأديبونكتين , و إنزيم الباروكسينيز .

وتم تقسيم هذه العينات من الاشخاص إلى ثلاث مجاميع تضم كل منها المجموعة الاولى: (الاشخاص ذوي الوزن الطبيعي, عددهم 80), المجموعة الثانية: (الاشخاص ذوي الوزن الزائد عددهم 58) ,المجموعة الثالثة: (الاشخاص البدينة, عددهم 62) .

أظهر التحليل الاحصائي باستعمال فحص الطالب–t زياده معنوية إيجابية ($P\leq 0.01$) في اللبتين , إنزيم الباروكسينيز , ونقصان معنوي في الأديبونكتين, الباروكسينيز , في الاشخاص ذوي الوزن الزائد و الاشخاص البدينة مقارنة بالأشخاص ذوي الوزن الطبيعي

لقد أظهر معامل الارتباط (r) بين هرمون اللبتين والمعايير الاخرى والذي اعتمد على مخطط الانحدار وجود علاقة إيجابية بين اللبتين مع (مؤشر كتلة الجسم ,نسبة الدهون في الجسم ,محيط الخصر) اللبتين , في حين أوضح وجود علاقة سلبية مع الأديبونكتين, الباروكسينيز , في الاشخاص ذوي الوزن الزائد و الاشخاص البدينة مقارنة بالأشخاص ذوي الوزن الطبيعي.

أظهرت نَتائِجُ Adiponectin ارتباطا إيجابياً مَع الباروكسينيز , بينما أظهرت ارتباط سلبي مَع (مؤشر كتلة الجسم ,نسبة الدهون في الجسم ,محيط الخصر) , اللبتين في الاشخاص ذوي الوزن الزائد و الاشخاص البدينة مقارنة بالأشخاص ذوي الوزن الطبيعي.

الاستنتاجات: الأديبونكتين كما الهرمون يلعب دورا هاما في الوقاية من الدهون، وبالتالي تصلب الشرايين ومضاعفاته في حين أشارت اللبتين بمثابة النتائج عوامل تصلب الشرايين. لقد دلت النَتائِجُ على وجود علاقة معنوية سالبة بين اللبتين مع الأديبونكتين و الباروكسينيز بينما علاقة معنوية موجبة بين الأديبونكتين مع الباروكسينيز .