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Study the Correlation of the Leptin to Adiponectin Ratio with Estimation of Insulin Resistance in Obese and Non Obese Individuals

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Abstract:
Background: Leptin to Adiponctin ratio (LAR) has been reported as potentially useful measure of insulin resistance (IR). Obesity is the dominant cause of insulin resistance. The concentration of leptin rises with obesity, whereas that of adiponectin decreases with obesity. We investigated whether LAR may serve as a better predictor than either leptin or adiponectin alone for (IR) and study the correlation between LAR and insulin in obese individuals.**Subjects and methods:** this study included 90 non-diabetic Iraqi males (45 obese with mean age (39.80±8.10) years old, range from (30-55) year and 45 non-obese individuals with mean age (42.0±7.04) years old, range from (31-54) year. Leptin, adiponectin and insulin were measured using enzyme linked immunosorbent assay technique (ELISA).**Results:** LAR, IR and leptin show significant highly increased in obese group compared to non-obese healthy subjects, while Adiponectin level show significant high decreased in obese group. The pearson correlation analysis found LAR had strong significant positive correlation with leptin ($r= 0.400$, $p<0.007$) and strong significant negative correlation with adiponectin ($r= -0.78$, $p<0.00$). **Conclusion:** the leptin-to-adiponectin ratio (LAR) correlates with insulin resistance better than either leptin or adiponectin levels alone.
Keywords: Lar, Ir, Leptin, Adiponectin and Obeaity.

Introduction:

Obesity results from an imbalance between food intake and energy expenditure which caused by excessive fat accumulation in adipose tissue, liver, muscle, pancreatic islets [(1)]. Over 60% of people in the United States are overweight or obese. It is well known that obesity is related with increased metabolic derangements include insulin resistance, hypertension, dyslipidemia [(2,3,4)], cardiovascular morbidity and mortality [(5)]. Although the mechanisms linking obesity and cardiovascular disease are not completely understood, recent study indicates insulin resistance has been play important role.

Insulin resistance (IR) is a pathological situation characterized by a lack of physiological response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances known as the metabolic syndrome [(6)]. The main features of this condition include dyslipidemia (high triglyceride and low HDL-cholesterol levels), hypertension, type 2 diabetes, hyperuricemia, abdominal obesity and defects in the fibrinolytic system, fatty liver, increased incidence of coronary heart disease and Insulin resistance is more strongly linked to intraabdominal fat than to fat in other depots [(6)]. Difficulties in measuring insulin sensitivity, however, prevent identification of insulin-resistant individuals in the general population. There are several methods to estimation insulin resistance(IR), for example ; Homeostasis Model Assessment for Insulin resistance (HOMA-IR)[(7)], hyperinsulinemic euglycemic clamp tests, Quantitative Insulin-Sensitivity Check Index (QUICKI)[(8)] and insulin suppression tests[(9)].

Recent research has recognized that adipose tissue is an active endocrine tissue, secreting several biologically active molecules, termed adipocytokines, which regulate body metabolism and the immune response. Leptin and adiponectin, the two major adipocytokines, respond in a reciprocal manner to increasing adiposity[(10)]. Which may contribute to insulin resistance [(11)].

Leptin is secreted by fat cells (adipocytes), and was originally thought it is signal to the brain to inhibit food intake and decrease weight [(12,13)]. This concept was partly driven by the observation that humans and rodents lacking a functional leptin protein or receptor manifested voracious feeding and obesity [(12)]. Leptin acts directly on the hypothalamus, thereby regulating food intake and energy expenditure [(14)]. Plasma leptin concentrations are significantly elevated in obese subjects in proportion to the degree of adiposity [(15),] suggesting that hyperleptinemia may play a role in the pathogenesis of obesity-related complications.

Adiponectin is an adipocyte-derived hormone with antiatherogenic, antidiabetic and anti-inflammatory properties. Its play an important a role in regulation of energy balance and peripheral tissue lipid metabolism [(16)]The mechanism by which adiponectin mediates enhanced insulin sensitivity appears to be linked mainly to rise fatty acid oxidation and glucose uptake via activation of adenosine monophospate activated protein kinase (AMPK)[(17).] Recently, the evaluation of leptin to adiponectin ratio has been proposed as a potential marker for assessing insulin resistance in obese subjects [(18)].

In the present study, we investigated whether LAR may serve as a better predictor than either leptin or adiponectin alone for insulin resistance and study the correlation between LAR and insulin resistance in obese and non obese individuals.

Subjects and methods:

A total of 90 males subjects (45 obese and 45 non-obese healthy control) were enrolled in our study from January 2013 to may 2014 with mean age of 39.80±8.10 year [range 30-55] in obese and mean age 42 ± 7.042 yr [range 31-54] in non-obese healthy control.

The exclusion criteria included any history of chronic or acute heart, renal, liver, diseases and diabetes mellitus.

Venous blood (10 ml) was collected from the study subjects after overnight fasting; serum was separated and store at -8 0C and analyzed later.

All measurements were performed in Baghdad teaching hospital (the teaching laboratories) which consists of measuring serum glucose, HDL-cholesterol by enzymatic method using spectrophotometer and serum leptin, adiponectin and insulin measured by using immunoassay method (ELISA).

Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index according to the following formula:HOMA-IR = [fasting serum insulin ((μIU/mL) × fasting plasma glucose (mg/dl)/405].[19]

The blood pressure was measured on the upper arm, with the subjects in a seated position after resting for 10 min.

Weight and height were measured in light clothing, no footwear and after 12 hour of fasting.

Body mass index (BMI) was measured according to the following equation: weight (kg)/height ^{2}(cm^2). Waist circumferences were measured to the nearest centimeter at the midpoint between the lower limit of rib cage and iliac crest. Obesity was defined as BMI ≥ 25 kg/m^2.

All results were expressed as the mean± standard deviation (SD). The differences between the obese and non-obese subjects were analyzed by a two-tailed student's t-test.

Results:

The general characteristic of the subjects which included in this study are demonstrated in table1. The mean levels of BMI, insulin, leptin, LAR (leptin to adiponectin ratio) and IR (insulin resistance) were highly significant increased ($p<0.00$) in obese subjects compared to healthy control while, the mean level of adiponectin was highly significant decreased ($p<0.00$) in obese group.

In the present study there was no significant difference between in the level of age, SBP, DBP, TG, HDL and FBG) between obese and non-obese healthy control.

Pearson correlation analysis of the present study was shown in table2 which found that the LAR had strong significant positive correlation with leptin ($r= 0.400$, $p<0.007$) and strong significant negative correlation with adiponectin ($r= -0.78$, $p<0.00$).

As well as, the insulin resistance show strong significant positive correlation with insulin and FBG ($r=0.837$,$p<0.00$,$r=0.552$,$p<0.00$) respectively. Also insulin resistance show significant negative correlation with age ($r=-0.308$, $p<0.0400$).

On the other hand, leptin show significant negative correlation with age ($r= -0.333$, $p<0.025$). In the present study triglyceride show significant negative correlation with HDL and FBG ($r= -0.495$, $p<0.001$, $r= -0.359$, $p<0.015$).

Multiple linear regression analysis with insulin resistance as dependent variable was shown in table3 which found the insulin and FBG were the significant establish, while the multiple linear regression with LAR as dependent variable was shown in table 4 which found the leptin ,age and adiponectin were significant establish.

The correlation coefficient for LAR with IR (beta=-0.056, R^2 =0.997), while the correlation coefficient for IR with LAR was (beta= -1.553, R^2 =0.905).

Table 1: the general characteristics of obese and non-obese healthy

Variable	Obese group n=45	Non-obese Control n=45	P-value
Age (years)	39.80±8.10	42.0±7.04	0.17
BMI(kg/m^2	27.09±1.72	23.91±1.30	0.00**
SBP(mmHg)	121.38±2.40	120.93±2.35	0.37
DBP(mmHg)	80.49±2.22	80.76±2.53	0.59
TG(mg/dl)	114.5±20.68	106.49±23.61	0.09
HDL-C(mg/dl)	47.18±5.72	50.22±6.99	0.02*
Insulin (µIU/ml)	22.22±3.28	7.68±1.85	0.00**
FBG(mg/dl)	80.0±9.74	84.04±9.54	0.05*
Leptin(ng/ml)	6.39±1.06	3.41±0.64	0.00**
Adiponectin (µg/ml)	4.46±1.07	8.59±1.25	0.00**
LAR	1.53±0.53	0.40±0.09	0.00**
Insulin resistance	4.38±0.82	1.58±0.39	0.00**

Table 2: pearsons correlation analysis between leptin, adiponectin , IR, LAR and other variables in obese group.

	leptin		adiponectin		Insulin		LAR		Insulin resistance	
	r	p	r	p	r	p	r	p	r	p
Age	-0.33	0.02	-0.17	0.24	-0.08	0.59	-0.12	0.39	-0.30	0.04
BMI	0.07	0.60	0.022	0.88	0.88	0.03	0.08	0.57	0.005	0.97
SBP	-0.16	0.28	0.19	0.19	-0.11	0.44	-0.28	0.06	0.06	0.66
DBP	-0.15	0.31	0.12	0.43	-0.23	0.11	-0.14	0.33	-0.06	0.66
TG	0.14	0.32	0.02	0.89	0.02	0.89	0.03	0.82	-0.18	0.23
HDL	0.27	0.06	-0.14	0.35	0.02	0.88	0.27	0.06	0.001	0.99
insulin	0.23	0.12	-0.02	0.87	1	------	0.16	0.27	0.83	0.000
FBS	-0.04	0.77	0.27	0.06	0.01	0.94	-0.26	0.07	0.55	0.000
Leptin	------	-------	0.12	0.42	0.23	0.12	0.40	0.007	0.15	0.30
Adiponectin	0.12	0.42	-----	-------	-0.02	0.87	-0.78	0.000	0.13	0.39
LAR	0.40	0.007	-0.78	0.000	0.16	0.27	----	----	-0.02	0.89
IR	0.15	0.30	0.13	0.39	0.83	0.000	-0.02	0.89	----	----

* Correlation is significant at 0.05 levels.
** Correlation is highly significant at 0.01 levels.

Table 3: multiple linear regression analysis with insulin resistance as dependent variable Including the other variable as independent in obese group.

Independent variable	LAR	P-value
	Beta	
Age	-.213-	.005
BMI	.033	.555
SBP	-.046-	.469
DBP	.051	.485
TG	-.061-	.511
HDL-C	.012	.890
Insulin	1.334	.076
FBG	.712	.144
Insulin resistance	.397	.000

Table 4: multiple linear regression analysis with LAR as dependent variable including the other variable as independent in obese group

Independent variable	Insulin resistance	P-value
	Beta	
Age	-0.024	0.116
BMI	0.001	0.898
SBP	-0.012	0.301
DBP	-0.006	0.640
TG	-0.015	0.409
HDL-C	-0.005	0.753
Insulin	0.834	0.000
FBG	0.530	0.000
LAR	0.006	0.764

Discussion

Adiponectin and leptin are the two major adipokine which mediate metabolic and cardiovascular complications associated with obesity which thought they play important roles in the regulation of obesity and cardiovascular disease. Leptin is one of a major adipocytokine which regulates energy expenditure and the intake of the food [(20)]. The results in this study show significantly increased in the concentration of leptin in obese subjects compared with healthy controls this results was agreement with considine et al[(15)]. Who found significantly elevated in leptin concentration in obese group in proportion to degree of adiposity.

Few study suggest that leptin rises glucose uptake and metabolism in skeletal muscle by activated 5-AMP protein kinase-(AMPK) dependent pathway[(21)]. Although leptin was reported to be a "good" hormone because it improves insulin resistance, obese individuals tend to have unusually increased circulating concentration of leptin as a result of leptin resistance [(22)]. These findings make our suggesting that hyperleptinemia may play a key role in pathogensis of obesity-related complications. Adiponectin raises tissue fat oxidation, which leading to decreased levels of fatty acid and triglyceride content in the tissue, thus raises the insulin sensitivity [(23)]. Adiponectin an anti-inflammatory adipocytokine appears to play a key role in regulation of energy balance and peripheral tissue lipid metabolism [(24)]. The molecular mechanism by which it mediates enhanced insulin sensitivity appears to be linked mainly to increase fatty acid oxidation and glucose uptake by activated of adenosine mono-phospate activation protein kinase (AMPK) [(25)]. Our study also show plasma adiponectin was significantly lower in obese subjects as compared to healthy individuals which is agreements with few study found significantly decrease in adiponectin level in obese compared to non-obese group [(26)]. Arita et al [27] demonstrated that plasma adiponectin levels were decreased in obesity subjects that make us suggesting that hypoadiponectinemia is involved in the pathophysiology of obesity. In the present study found the level of leptin to adiponectin ratio (LAR) were significantly higher in obese than non-obese group. These results are agreement with Satoh et al [28] and Kotani et al [29] who found the leptin are increased and adiponectin levels are decreased, thus the ratio of leptin to adiponectin could be relatively also high. This fact which can explains the results obtained by this study.

In our study adiponectin level not show significant negative correlation with insulin and insulin resistance these finding which disagreement with Mojiminiyi et al[(30)] who demonstrated that adiponectin was show significant inverse correlation with insulin resistance as measured by HOMA which depends on that the higher levels of insulin in insulin resistant subjects may down regulate level of adiponectin [(31)].

The present study also show significant high positive correlation between insulin with insulin resistance this finding was consistent with Nada F [(32)] which demonstrated significant positive correlation between insulin resistancewith insulin.

Furtheremore, we finding significant association not previously reported between FBS with insulin resistance and TG.

The observed increase in LAR in obese as compared to the increase in HOMA-IR may suggest that LAR could be a useful marker for insulin resistance in clinical practice.

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