Research Article

Adiponectin to Leptin ratio as marker for Insulin Resistance in Diabetic Males in relation to Glycemic Control

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Abstract

Background and Aims: recently it has been established that abnormal adipocytokines may contribute to insulin resistance in diabetes. The current study designed to investigate adiponectin to leptin ratio (A/L) as a reliable marker for insulin resistance in good and poor glycemic controlled type 2 diabetics.

Patients and Methods: A total 120 males were recruited in the study, out of them there were sixty persons with type2 diabetes (29 of them with good glycemic control, and 31 with poor glycemic control), there were sixty persons serves as healthy controls. They were matched for age, and BMI. Fasting venous blood samples were collected for measuring fasting serum glucose (FSG), glycated hemoglobin (HbA1c), and lipid profile, insulin, adiponectin, and leptin. Blood pressure, waist circumference, and BMI were determined for all participants. Homeostasis model assessment (HOMA)-insulin resistance (IR) index, and adiponectin/leptin ratio (A/L) ratio were calculated.

Results: the result showed a significant decline in adiponectin, and A/L ratio, and a significant rise in serum leptin, insulin, HOMA-IR, FSG, HbA1c, and serum triglycerides TG in diabetes group as compared to healthy control group. On the other hand, correlation analysis revealed that A/L ratio is the most likely markers that closely linked with insulin resistance parameters than HOMA, adiponectin, and leptin; even after multiple regression analyses, it was correlated more than HOMA-IR with insulin resistance parameters. When patients were divided according to their glycemic control (poor and good controlled), the result showed a lowered adiponectin, and A/L ratio; as well as, there was a significant increase in serum leptin, insulin, and HOMA-IR in poorly controlled compared to good-controlled diabetes group. On the other hand, the correlation coefficient investigated to show the relation between both (A/L ratio, and HOMA-IR) and other variables in each group of glycemic control; and observed that A/L ratio has a strong significant correlation with other parameter than HOMA-IR in both groups.

Conclusions: the results suggested that the A/L ratio was more linked with insulin resistance parameters than HOMA-IR. In addition to that, A/L ratio is a good predictor for insulin resistance in good and poorly controlled diabetes mellitus. Accordingly, an A/L ratio is likely to become a new laboratory biomarker of insulin resistance.

Keywords: Adiponectin/leptin ratio, glycemic control, insulin resistance, Type 2 diabetes

INTRODUCTION

Type2 diabetes mellitus is characterized by insulin resistance rather than absolute insulin deficiency.[1] Insulin resistance is associated with obesity as well as hypertension, coronary artery disease, and dyslipidemias.[2] There are many ways to measure insulin resistance, for example; Homeostasis Model Assessment for Insulin resistance (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI), hyperinsulinemic euglycemic clamp tests and insulin suppression tests.[3]

Insulin resistance is more strongly linked to intra-abdominal fat than to fat in other depots, and Adipose tissue besides being a source of energy for body is now well recognized as an endocrine organ, playing an important role in modulating insulin activity, inflammation and vascular thrombosis.[4] Recent research has demonstrated that adipose tissue is an active endocrine tissue, which secretes hormones such as leptin and adiponectin, referred to as adipocytokines,[5] which may contribute to insulin resistance.[6]

Leptin, regulates body weight, modulates insulin activity and sensitivity, metabolism and reproductive function.[7] Leptin resistance is related to development of insulin resistance in individuals of type2 diabetes,[8] the exact relationship between leptin and insulin is not clear and is sometimes controversial.

Adiponectin an anti-inflammatory adipokine appears to have a role in regulation of energy balance and peripheral tissue lipid metabolism.[9] The molecular mechanism by which it mediates enhanced insulin sensitivity appears to be linked mainly to increase fatty acid oxidation and glucose uptake via activation of adenosine monophospate activated protein kinase (AMPK)[10] thereby directly regulating glucose metabolism and insulin sensitivity. Adiponectin appears to be linked to glucose homeostasis since plasma adiponectin levels are lower in diabetic subjects.[4, 11] Hypoadiponectinemia was found to be an independent risk factor for progression to type 2 diabetes.[12]

More recently, the evaluation of the adiponectin/leptin ratio has been suggested as a useful parameter for assessing insulin resistance in patients with and without diabetes.[13-16] Inoue et al.[13, 14] reported that the adiponectin/leptin (A/L) ratio was more effective as a parameter of insulin resistance than single adipokines and was a more sensitive and reliable marker of insulin resistance than was homeostasis model assessment (HOMA)-insulin resistance (IR) in subjects without hyperglycemia, as well as in type 2 diabetes patients. Recently published studies support the previous results on the association of A/L ratio with insulin resistance.[15, 16]

A few studies have reported association of adipocytokines with glycemic control;[17, 18] however, scare or no information is available regarding the adiponectin/leptin ratio (A/L) in good and poor glycemic control. Therefore, the present study planned to consider serum leptin, adiponectin, and A/L ratio, and HOMA-IR in patients with and without type2 diabetes. As well as, to consider whether the A/L ratio is a better predictor for insulin resistance compared to HOMA-IR in good and poor glycemic control.

PATIENTS AND METHODS

A total of one hundred twenty males subjects were enrolled in this study, divided into Group1 consist of sixty males subjects who were previously diagnosed type2 diabetic patients attending to the National Diabetes Center (Al-Mustansiyriah University) Baghdad, Iraq. They were further divided into two groups according to their mean galycated hemoglobin (HbA1c), and fasting serum glucose (FSG) values, as good controlled (G1(A)[29 patients]) (had HbA1c<7%, and FSG <110 mg/dl) and poorly controlled (G1(B)[31 patients]) (had HbA1c≥7%, and FSG≥110) patients with DM. Finally sixty males subjects serves as a healthy control defined as Group2 Diabetic and control groups were confirmed to have no known other diseases (including cardiovascular disease, thyroid disease, hypertension or any other acute and chronic disease condition, and any current infectious condition). Patients suffering from type 1 diabetes mellitus, smoker, and any known mental illness were excluded. The patients with type 2 diabetes who were included in the study were being treated by dietary means or with sulphonylurea an oral hypoglycaemic agent. Patients being treated with insulin and metformin were excluded, because of the effect of these therapies on adipokines.[19]

All subjects were matched for age, and BMI. Weight and height were measured in indoor clothing without shoes, and the BMI was calculated as weight (kg)/height^2 (m^2). Waist circumferences were measured in a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest. Blood pressure was measured twice on the right arm using standard mercury

sphygmomanometer while the patient was sitting after resting for 10 min.

Blood samples were taken after overnight fasting; serum was separated, store at -8 0C, and were analyzed at later time. Laboratory evaluations consisted of measuring glycemic control including (fasting serum glucose (FSG), glycated hemoglobin HbA1c), lipid profile [total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), and low density lipoprotein (LDL), insulin, Adiponectin, and leptin were measured.

Hemoglobin A1c program intended for the determination of Glycated hemoglobin (A1c) in human depended on high performance liquid chromatography and who supplied by Variant Company, USA. Glucose level was determined using kits supplied by Randox, UK. Total cholesterol TC, Triglycerides, High density lipoprotein (HDL) was determined using kits from (biomaghreb, Sa, France). Low density lipoprotein (LDL) was calculated mathematically using the Friedwald formula.

Leptin (L) assay: done by the DRG Leptin Enzyme Immunoassay Kit (ELISA) provides materials for quantitative determination of leptin. Adiponectin(A) assay: done by the human adiponectin ELISA kit (DRG, USA) is used for non–radioactive quantification of human adiponectin.

Insulin (Ins) assay: done by the DRG Insulin Enzyme linked Immunosorbant Assay Kit (ELISA) provides materials for the quantitative determination of insulin. The assay is intended for in vitro diagnostic use only. HOMA IR was calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA-IR= [fasting serum insulin (µU/ml) × fasting plasma glucose (mg/dl)/405].[20]

Statistical analysis: Data were analyzed using computer facility-the available statistical packages of SPSS-17.0 (statistical packages for social sciences-version 17.0). All continuous variables are shown as mean ±SD. The significance of difference between quantitative variables was tested using student t-test for comparing between two means of independent groups. P value equal and less than 0.05 was used as the level of significance, and P value equal and less than 0.01 was used as the level of a highly significant. Pearson correlations coefficient were used to analyze the relationship between variables, which is significant at the 0.05 level (2-tailed).

Multiple linear regression analyses were conducted to determine the predictor for A/L ratio and HOMA-IR after adjustment for confounding variables.

RESULTS

The general characteristic of the study patients and control were presented in table1, which showed that patients and controls were matched for age, and BMI. There was a significant decrease in adiponectin, and A/L ratio in diabetes group as compared to that in control group (8.45 ± 1.97 vs 15.43 ± 3.91 $p<0.01$; 0.89 ± 0.08 vs 2.71 ± 0.18 $p<0.05$) respectively. On the other hand, there was a highly significant increase in serum leptin, insulin, and HOMA-IR in diabetic patients compared to healthy control group (16.89±4.59 vs 7.56 ±1.54; 14.65 ± 3.67 vs 8.89 ± 2.31; 6.98 ±1.03 vs 2.1 ± 0.27, $p<0.01$) respectively. Moreover, there was a significant increase in serum FSG, HbA1c, TG in diabetic patients compared to control group (170.1± 18.84 vs 95.25±15.18 $p<0.001$; 8.79 ± 2.46 vs 5.19 ±0.89 $p<0.01$; 176.98 ±16.7 vs 127.88 ±15.34 $p<0.05$). Although, there was no significant differences between patients and control group in levels of (SBP, DBP, TC, HDL, and LDL).

Table 1. The general characteristics of patients and control

	G1:Patients	G2:Control
No.	60	60
Age, yrs	46.9±11.28	46.3 ±12.01
BMI (kg/m^2)	24.52±4.63	24.08 ±2.98
WC (cm)	97 ± 2.3	102 ± 4.1
SBP (mmHg)	129.3±17.1	120 ± 16.89
DBP (mmHg)	79.3 ± 11.5	71.3 ± 11.01
FSG (mg/dl)	170.1± 18.84**	95.25±15.18
HbA1$_c$	8.79 ± 2.46**	5.19 ±0.89
TC (mg/dl)	178.5 ± 18.86	166.17± 15.34
TG (mg/dl)	176.98 ±16.7*	127.88 ±15.34
HDL-C (mg/dl)	39.66 ±8.46	40.99 ± 9.34
LDL-C (mg/dl)	124.7±21.45	115.3± 20.34
Insulin (µIU/ml)	14.65 ± 3.67**	8.89 ± 2.31
HOMA-IR	6.98 ±1.03**	2.1 ± 0.27
Leptin (ng/ml)	16.89±4.59**	7.56 ±1.54
Adiponectin (µg/ml)	8.45 ± 1.97**	15.43 ± 3.91
A/L ratio	0.89 ± 0.08*	2.71 ± 0.18

Data are mean ± SD, *P<0.05 was considered significant, and **P<0.01 is a highly significant.

Pearson correlation analysis was used to identify the insulin resistance parameters and other variables that most closely related to the hormones adiponectin/leptin ratio, HOMA-IR, adiponectin, and leptin as shown in Table2. Which showed that A/L ratio had strong significant negative correlations with (BMI, WC, FSG, HbA1c, TG, insulin, HOMA-IR, leptin) (r= -0.621, -0.745, -0.651, -0.56, -0.489, -0.861, -0.631, -0.601, p<0.01) respectively. As well as, there was a significant positive correlation between A/L levels and both of Adiponectin, and HDL (r=0.798, p<0.01; r=0.320, p<0.05) respectively. HOMA-IR showed significant positive correlation with (BMI, FSG, TG, insulin, and leptin) (r= 0.312, p<0.05; r=0.495, p<0.01; r=0.391, p<0.01; r= 0.707, p<0.01; r= 0.298, p<0.05) respectively, and negative correlation with adiponectin (r=-0.401, p<0.01. On the other hand, Adiponectin showed negative correlation with TG, and leptin levels (r= -0.289 p<0.05; and r= -0.399, p<0.01 respectively), and showed a significant positive correlation with HDL (r= 0.431, p<0.01). While, leptin levels showed significant positive correlation with (BMI, WC, FSG, TG, and insulin) (r=0.562, r=0.512, r= 0.307, r=0.403, r=0.641) respectively.

Table 2. Correlation analysis between HOMA-IR, Adiponectin, leptin, A/L ratio and variables in patients

	A/L ratio	HOMA-IR	Adiponectin	Leptin
	r	r	r	r
Age	0.123	-0.035	+0.101	-0.064
BMI	-0.621**	0.312*	-0.15	0.562**
WC	-0.745**	0.098	-0.185	0.512**
SBP	-0.091	0.195	-0.045	0.043
DBP	-0.063	0.201	-0.021	0.019
FSG	-0.651**	0.495**	-0.198	0.307*
$HbA1_c$	-0.560**	0.102	-0.121	0.131
TC	-0.104	0.123	-0.096	0.098
TG	-0.489**	0.391**	-0.289*	0.403*
HDL-C	+0.320*	-0.198	0.431**	-0.021
LDL-C	-0.062	-0.065	-0.028	0.191
Insulin	-0.861**	+0.707**	-0.150	0.641**
HOMA-IR	-0.631**	-	-0.401**	0.298*
Leptin	-0.601**	0.298*	-0.399**	-
Adiponectin	0.798**	-0.401**	-	-.399**
A/L ratio	-	-0.631**	0.798**	-.631**

*correlation is significant at the 0.05 level (2-tailed)
**correlation is a highly significant at the 0.01 level (2-tailed)

Table 3. Multiple linear regression analysis with A/L ratio or HOMA-IR as the dependent variable including the some variable as independent

Independent variable	A/L ratio	HOMA-IR
	Beta	Beta
Age	0.012	-0.041
BMI	-0.549**	-0.011
WC	-0.852**	0.023
FSG	-0.761**	0.634**
HbA1c	-0.198*	0.038
TG	-0.799**	-0.632**
TC	0.023	0.051
Insulin	-0.289*	0.239*
HOMA-IR	-0.297*	-------
A/L ratio	-------	-0.236*

(R^2 for A/L ratio is 0.681) ; (R^2 for HOMA-IR is 0.501)

*P<0.05 was considered significant, and **P<0.01 is a highly significant.

Table 3 shows multiple linear regression analyses with A/L ratio or HOMA-IR as the dependent variable, including each variable in the conflicting model, as well as other variables as independent. When the analysis was executed with A/L ratio as the dependent variable; the BMI, WC, FSG, HbA1c, TG, insulin, and HOMA-IR were the significant establish. While, when the analysis was executed with HOMA-IR as the dependent variable; the FSG, TG, insulin, and A/L ratio were the significant establish. The correlation coefficient for A/L with HOMA-IR was (-0.297, R2 = 0.681). While, the correlation coefficient for HOMA-IR with A/L ratio was (-0.236, R2 = 0.501).

In table 4 patients were divided into 2 groups classified according to their glycemic control including (FSG, and HbA1c), which demonstrated that adiponectin, and A/L ratio in poorly controlled diabetes group was significantly lower than that in good-controlled diabetes group (6.45± 0.87 vs 10.12 ± 2.01, p<0.05; 0.68 ± 0.07 vs 1.39 ± 0.09, p<0.01) respectively. On the other hand, there were significant increases in (WC, TC, TG, insulin, HOMA-IR, and leptin levels) in poor control diabetic patients compared to well control diabetic patients (104 ± 2.7 vs 96 ± 2.02, p<0.01; 181.88±16.19 vs 167.62±15.2, p<0.05; 198.36±19.07 vs 160.31 ±14.1, p<0.05; 16.87 ± 5.89 vs 9.98 ± 3.76, p<0.01; 7.95 ± 1.89 vs 3.73 ± 0.15, p<0.01; 18.65 ± 4.92 vs 13.01 ± 3.32, p<0.05) respectively.

Table 4. The general characteristics of patients according to glycemic control group

Clinical characteristics	Type 2 DM	
	G1(A)	G1(B)
No.	29	31
Age (yrs)	46.6±10.3	47.01± 12.4
BMI (kg/m^2)	24.21±5.6	24.73±3.5
WC (cm)	96 ± 2.02**	104 ± 2.7
Duration (yrs)	7.98±0.8*	10.1± 1.2
SBP (mmHg)	128.8 ± 16.3	130.01 ± 18.4
DBP (mmHg)	75.3 ±10.4	77.1 ± 11.9
FSG (mg/dl)	103.3±16.23**	189.91±22.58
HbA1$_c$ (%)	6.21± 0.9**	9.1 ± 1.2
TC (mg/dl)	167.62±15.2*	181.88±16.19
TG (mg/dl)	160.31 ±14.1*	198.36±19.07
HDL-cholesterol (mg/dl)	40.1 ± 8.83	39.05 ± 7.32
LDL-cholesterol (mg/dl)	123.8 ± 20.34	125.98 ± 21.99
Insulin (µIU/ml)	9.98 ± 3.76**	16.87 ± 5.89
HOMA-IR	3.73 ± 0.15**	7.95 ± 1.89
Leptin (ng/ml)	13.01 ± 3.32*	18.65 ± 4.92
Adiponectin (µg/ml)	10.12 ± 2.01*	6.45± 0.87
A/L ratio	1.39 ± 0.09**	0.68 ± 0.07

Data are mean ± SD, *P< 0.05 was considered significant, and **P<0.01 is a highly significant.

Table5 investigated the pearson correlation coefficient between variables and both of (A/L ratio, and HOMA-IR) in each group of glycemic control. Strong significant correlations between the parameters and A/L were tended to be observed in both groups; however, the significant correlations between the parameters and HOMA-IR were no longer observed in both groups.

DISCUSSION

Leptin and adiponectin are important hormones derived from fat cells and secreted into the serum. Both hormones improve insulin resistance.[8, 21] It was reported that the ratio of leptin to adiponectin (A/L) could act as a useful marker for metabolic disease.[22] Indeed, A/L was reported to display a better correlation to insulin resistance than the level of leptin or adiponectin alone.[13, 14] The present study, tried to avoid possible bias or confounders, by choosing a homogenous cohort made up of non-obese persons healthy and patients with T2DM who were of the same sex and BMI~24 Kg/m2 because of the influence of these factors on plasma leptin and adiponectin.

Table 5. Correlation analysis between A/L ratio, HOMA-IR, and variables in patients according to glycemic control

Parameters	G1 (A)		G2 (B)	
	HOMA-IR	A/L ratio	HOMA-IR	A/L ratio
	r	r	r	r
BMI	0.324	-0.560**	0.397*	-0.592**
WC	0.034	-0.360	0.051	-0.397*
FSG	0.386*	-0.579**	0.401*	-0.582**
HbA1c	0.210	-0.450*	0.120	-0.434*
TG	0.154	-0.572**	0.561*	-0.581**
HDL	-0.012	0.401*	-0.021	0.412*
Insulin	0.385*	-0.398*	0.390*	-0.388*
HOMA-IR	------	-0.431*	------	-0.441*
Leptin	0.167	0.331	0.143	0.391*
Adiponectin	-0.396*	-0.410*	-0.399*	-0.401*
A/L ratio	-0.431*	------	-0.441*	------

*correlation is significant at the 0.05 level (2-tailed)

**correlation is a highly significant at the 0.01 level (2-tailed)

The present study demonstrated a significant decrease of the serum adiponectin levels in the diabetic patients compared to healthy control group. Reduced adiponectin is related to impaired insulin action in type 2 diabeticts.[23] Adiponectin concentration was significantly associated with insulin sensitivity.[23] Another finding in the current study showed that adiponectin has an inverse correlation with insulin resistance as measured by HOMA, this is similar to the result of Mojiminiyi etal,[24] which shown that levels of adiponectin are strongly correlated with insulin sensitivity and low adiponectin was found in patients with IR. The precise mechanisms of the association between adiponectin, insulin and IR have not been fully explicated, there is indication that insulin may have direct effect on adiponectin gene expression and adiponectin concentrations in vitro.[25] It is therefore imaginable that the higher levels of insulin in insulin-resistant subjects may down regulate levels of adipo¬nectin as suggested previously[26] On the same side, the current data demonstrated no significant negative relationship between insulin and adiponectin. The present study showed that poorly controlled diabetics had lower adiponectin levels and also had higher insulin resistance as measured by (HOMA-IR), this result is in disagreement with other investigator.[17] But Koerner et al.[27] confirmed that lower adiponectin in uncontrolled type 2 diabetes increases the risk of

complication. Although, the present study found a significant relationship between insulin resistances as measured by HOMA-IR and adiponectin in both groups.

The current study demonstrated that leptin levels were higher in diabetic subjects than healthy control, this is in agreement with previous study.[28] Another finding in the present study observed a significant increased plasma level of leptin in poorly-controlled DM compared to the good-controlled DM, this is in disagreement with other.[17] But the current results are in agreement with Ajala etal[18], and confirm the finding of Wu etal.[28] who established that leptin levels are elevated in diabetic patients which had hyperinsulinaemia and insulin resistance (poor glycemic controlled) than in healthy persons.

The increased leptin levels in the poorly-controlled DM may be due to elevated plasma triglyceride concentrations which may lead to expansion of the volume of fat cells in non-controlled T2DM persons, which may lead to an increase in ob gene expression and serum leptin concentrations. In addition, it is possible that plasma triglyceride concentrations are affected by leptin, through indirect method involved in insulin resistance;[29] however, the current study showed a significant positive correlation between leptin and TG in diabetic patients.

Moreover, the current study showed that there was positive correlation between the degree of insulin resistance as measured by HOMA-IR and leptin levels in type2 diabetic patients. It has been demonstrated by different studies that hyperleptinemia is an independent risk factor for progression of insulin resistance in type 2 diabetes.[30, 31]

Another finding in the current study was negative correlation between leptin and adiponectin levels, this disagree with Zahra et al.[17] But agree with other.[32] Thorand et al.[33] showed a significant interaction between both adipokines in the multivariable adjusted model statistical analysis. The current study showed that A/L ratio is correlated strongly with insulin resistance parameters such as (BMI, WC, TG, HDL, FSG, insulin) compared with HOMA-IR, which is in agreement with other previous study.[16] Moreover, in multiple regression analysis, A/L ratio and HOMA-IR affected each other and were significant predictors for each other, suggesting that A/L ratio might be used as an insulin resistance marker in type 2 diabetic. However, as expected from the multiple linear regression analyses, revealed that when A/L used as the dependent variable the results showed significantly higher correlations with other metabolic variables compared with results from using HOMA-IR as the dependent variable. Therefore, the current study conclude that A/L could be a stronger marker for insulin resistance in type 2 diabetic patients than HOMA-IR, this result is in agreement with other studies results,[13, 14] previous study has suggested that A/L ratio was significantly associated with clamp-derived insulin sensitivity index, as well as that A/L ratio is an even stronger predictor for insulin sensitivity than are other insulin sensitivity indices, such as HOMA and QUICKI.[34] Thus, it is supposed that A/L influence directly in the progression of type 2 DM (if insulin resistance is considered as a factor of diabetes mellitus pathogenesis).

On the other hand, leptin and HOMA-IR were significantly higher and Adiponectin and A/L ratio were significantly lower in patients with poor glycemic controlled compared to good glycemic control, which is in agreement with other.[35] However, limited or no information is available about the A/L during good and poor glycemic control. Highly interesting is the fact that A/L ratio in type 2 DM, and in both group of glycemic control was correlated negatively with HbA1c, and FSG. Thus, the data confirm that A/L ratio may be related to diabetes control.

The result showed significant correlations between the insulin resistance parameters and A/L in poor and good control diabetic patients. On the other hand, the significant correlations between HOMA-IR and insulin resistance parameters were observed weakly in poor and good glycemic control. Katsuki et al.[36] demonstrate that neither HOMA-IR nor QUICKI should be used as an index of insulin resistance in elderly patients with poorly glycemic control type 2 diabetes mellitus, and elucidate that a different index of insulin resistance for this group of patients should be developed. Thus, the current study revealed that A/L ratio can be used as a new index for insulin resistance in poor glycemic control diabetic patients.

In conclusion the present study concluded that the ratio of Adiponectin/Leptin is well related with insulin resistance parameters in good and poor glycemic control diabetic patients. Thus, the data suggested that A/L ratio is a good predictor and a new index for insulin resistance and more useful than HOMA-IR to accurately assess insulin resistance in good and poorly controlled type2 diabetic patients.

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