Research Article

Role Of Leptin/Adiponectin Ratio In Iraqi Type 2 Diabetic Patients Treated With Different Antidiabetic Agents

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Abstract

Background: Leptin/adiponectin ratio has a potential additional value as a marker of central role of excess adipose tissue in insulin resistance, thus it contributes in the modulation of diabetes mellitus risk. Adipose tissue is involved in the regulation of energy balance and insulin action in type 2 diabetes mellitus patients.
Aim of this study: Study of the role of leptin/adiponectin ratio and its association with insulin resistance in type 2 diabetic patients treated with different oral antidiabetic agents.
Materials and Methods: Ninety patients with type 2 diabetes mellitus (45 males and 45 females) age between (35-60 years) and body mass index (<25) were enrolled in this study in addition to 40 healthy subjects matched with the patients for age, gender and body mass index. This study was conducted between March to December 2016 in the National Diabetes Center for Treatment and Research and Al-Yarmook teaching hospital/ Baghdad/ Iraq. We divided the patients into three groups according to medication option: Group I-include 30 type 2 diabetic patients treated with metformin alone, Group II-include 30 type 2 diabetic patients treated with glibenclamide alone, Group III-include 30 type 2 diabetic patients treated with metformin and glibenclamide. Blood samples were analyzed for fasting serum glucose, glycosylated heamoglobin, fasting serum insulin, total cholesterol, triglyceride, high density lipoprotein cholesterol, serum leptin, serum adiponectin, homeostasis model assessment of insulin resistance and leptin/adiponectin ratio.
Result: Fasting serum glucose, glycosylated heamoglobin, fasting serum insulin, insulin resistance, total cholesterol, triglyceride and serum leptin levels showed significant increase in diabetic patients when compared with control group ($p<0.05$). High density lipoprotein cholesterol and serum adiponectin levels showed significant decrease in diabetic patients ($p<0.05$), while leptin/adiponectin ratio was significantly higher for diabetics as compared with controls ($p<0.01$). Leptin concentration was significantly low as well as adiponectin concentration was significantly higher in type 2 diabetic patients treated with metformin alone (group I) when compared to those treated with glibenclamide alone (group II) or those treated with metformin plus glibenclamide (group III), while non-significant difference was noticed between (group II) and (group III). Homeostasis model assessment of insulin resistance in group I and III (patients treated with metformin as monotherapy or combination) showed a significant positive correlation with leptin and negative correlation with adiponectin ($p<0.01$), but non-significant correlation was recorded in group II (patients treated with glibenclamide alone). Correlation of homeostasis model assessment of insulin resistance with leptin/adiponectin ratio found to be significant in metformin treated groups ($p<0.05$) while non-significant with glibenclamide group.
Conclusion: Leptin/adiponectin ratio in type 2 diabetes mellitus can serve as an index of insulin resistance independent of body mass index. Leptin/adiponectin ratio can measure the usefulness of antidiabetic therapy based on insulin level and insulin sensitivity.

Key words: T2DM, Leptin, Adiponectin, LAR, Metformin, Glibenclamide.

INTRODUCTION

Adipose tissue acts as an active endocrine organ that can communicate with other organs via signaling molecules and bioactive mediators, termed as adipokines.[1] Via these adipokines, adipose tissue modulates hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis.[2] However, many of these physiological and pathological aspects seem to be related to the role of adipokines in obesity, since expansion of adipose tissue in obesity alters adipokines secretion which may contribute to the development of type 2 diabetes and metabolic diseases.[3,4]

Furthermore, it seems apparent that obesity represents one of the foremost contributory factors in the pathogenesis of type 2 diabetes that is mediated through the concurrent progression of insulin resistance and subclinical inflammation and seems to be related to the expression and functional properties of adipokines and their effects on metabolism, although the molecular mechanisms for this are less understood.[5,6]

Two major adipokines, leptin and adiponectin, are secreted from white adipose tissue and thought to play essential roles in the regulation of cardiovascular and metabolic homeostasis. Leptin; a 16 kDa protein; act as a satiety factor and an energy regulator.[7] Leptin, by acting directly on the hypothalamus, regulates food intake and energy utilization. Obesity found to elevate plasma leptin concentrations and reduced insulin sensitivity, suggesting that excess leptin level may play a role in the pathogenesis of obesity related complications.[8] Adiponectin; a 30 kDa protein; act as an insulin sensitizer and carbohydrate and lipid modulator. Adiponectin by acting on hepatic cells increase tissue fat oxidation, leading to decrease fatty acids and triglyceride levels, thus improving insulin sensitivity.[9] Paradoxically, plasma adiponectin concentrations are decreased in patients with obesity, suggesting that reduced adiponectin level is involved in the pathophysiology of obesity and obesity-linked diseases. [10]

Leptin/Adiponectin ratio (LAR) found to be associated with the components of metabolic syndrome and a preferential marker of cardiovascular event and insulin resistance, therefore can serve as a potential atherogenic index in obese type 2 diabetic patients as well as a useful indicator for the choice of drug to treat diabetes mellitus.[11,12]

Biguanides and sulfonylureas are two major groups of hypoglycemic medications that while function via different pathways, they are both effective in short- and long-term glucose control.[13] There is also evidence that these medications might alter adipokines secretion by direct and indirect ways.[14,15] The present study is designed to investigate the concentrations of serum leptin and adiponectin and their ratio (LAR) in type 2 diabetic patients treated with metformin (a bigunaide) and glibenclamide (a sulfonylurea) as monotherapy and as a combination.

PATIENTS AND METHODS

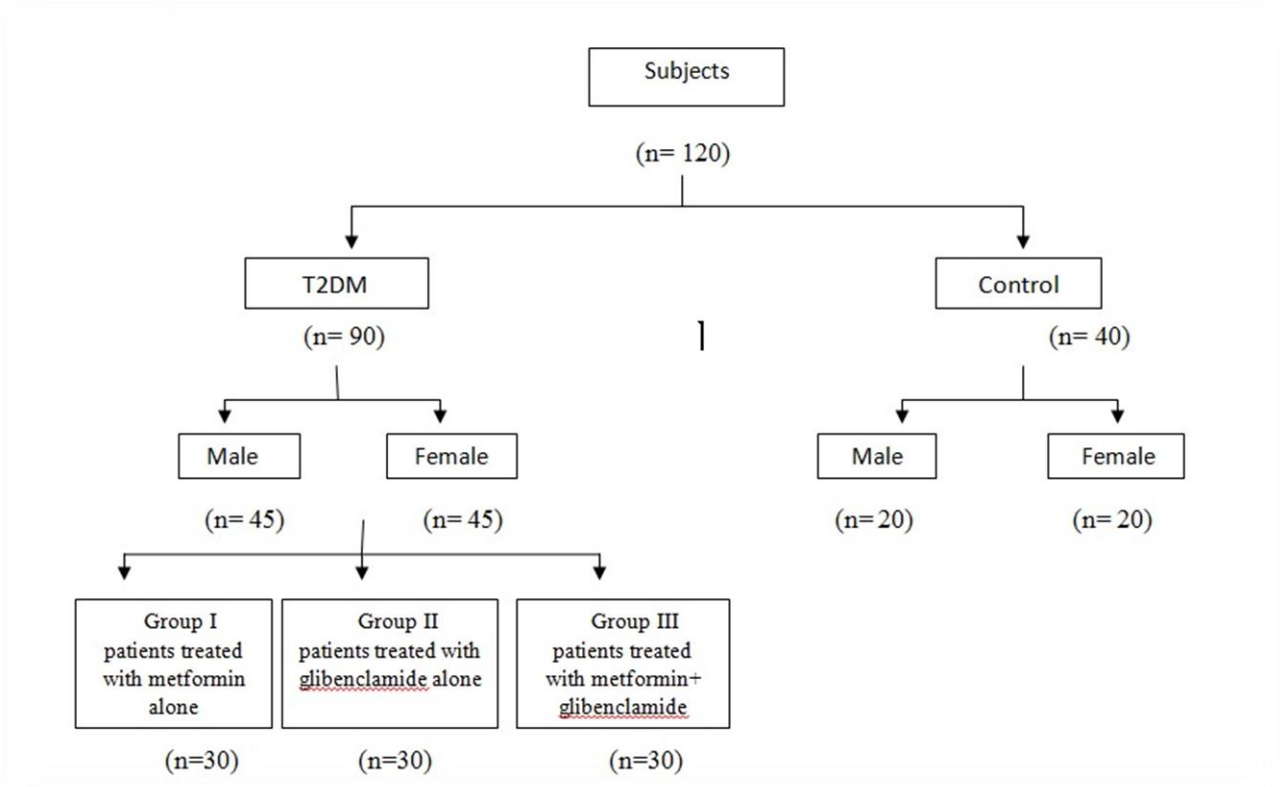
This randomized cross-sectional study conducted between March to December 2016 in the National Diabetes Center for Treatment and Research and Al-yarmook teaching hospital/ Baghdad/ Iraq. After approval from the scientific committee in the center, 90 patients with type 2 diabetes mellitus (T2DM) (45 males and 45 females) aged between (35-60 years) with BMI<25 were enrolled in the study in addition to 40 healthy subjects matched with the patients for age, gender and body mass index (BMI).

We included only the patients who treated with oral antidiabetic agents; either metformin, glibenclamide or both; for a period not less than 6 months and we exclude the patients who received any other medications that could affect on the measurements of the parameters. Therefore we divided the patients into three groups according to medication option:

Group I-include 30 T2DM patients treated with metformin (Glucophage® Merck, France) 500 mg tablet three times daily.

Group II-include 30 T2DM patients treated with glibenclamide (Glibil® Medochemie, Cyprus) 5 mg tablet daily.

Group III-include 30 T2DM patients treated with Glucophage®(500 mg tablet twice daily) and Glibil® (5 mg tablet daily).



After 12 hours of overnight fasting, blood samples were analyzed for fasting serum glucose (FSG), glycosylated heamoglobin (HbA1c), fasting serum insulin (FSI), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-c), serum leptin and adiponectin. Insulin resistance was evaluated by the homeostasis model assessment and expressed in HOMA-IR.

HOMA-IR score = FSG (mg/dL) × FSI (mg/dL)/405.[16]

Serum insulin, leptin and adiponectin concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (Demeditec Diagnostic, Germany). FSG was measured using enzymatic colorimetric method (Spinreact, Spain) and glycated hemoglobin levels (HbA1c) were determined by high-performance liquid chromatography (HPLC) (Bio-Rad Variant, Italy). Concentrations of TC, TG and HDL-c were determined by enzymatic techniques (Randox, UK) and (Spinreact, Spain) respectively. HDL-c levels were measured after precipitation of plasma apoB containing lipoproteins with phosphotungstic acid.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2007. Data are expressed as means ± standard deviation (SD). Differences between groups were compared by one-way analysis of variance (ANOVA). A p-value of <0.05 was considered as significant.

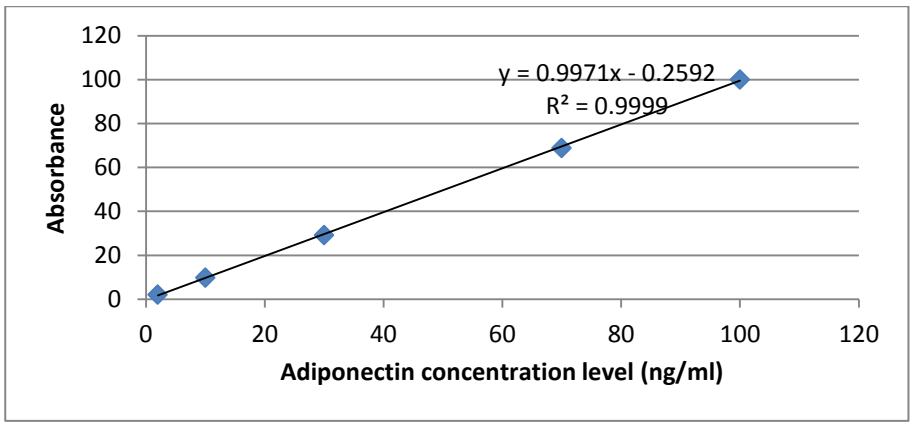


Figure 1: **Standard curve of Adiponectin.**

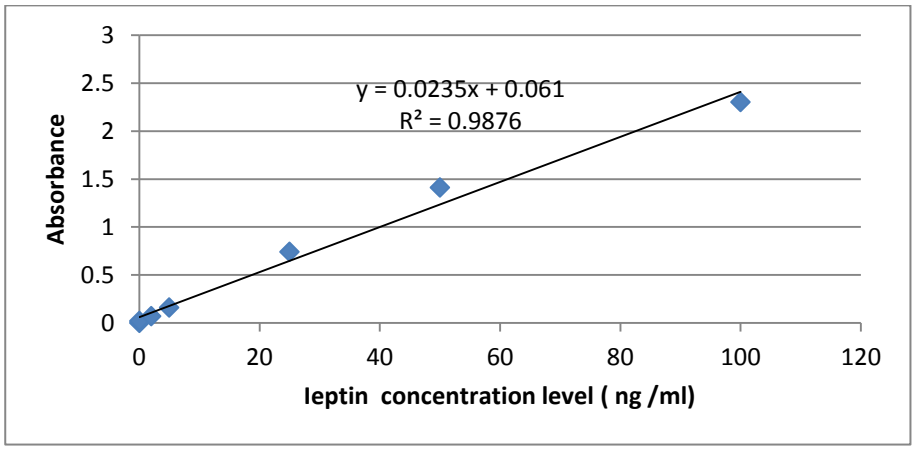


Figure 2: **Standard curve of Leptin.**

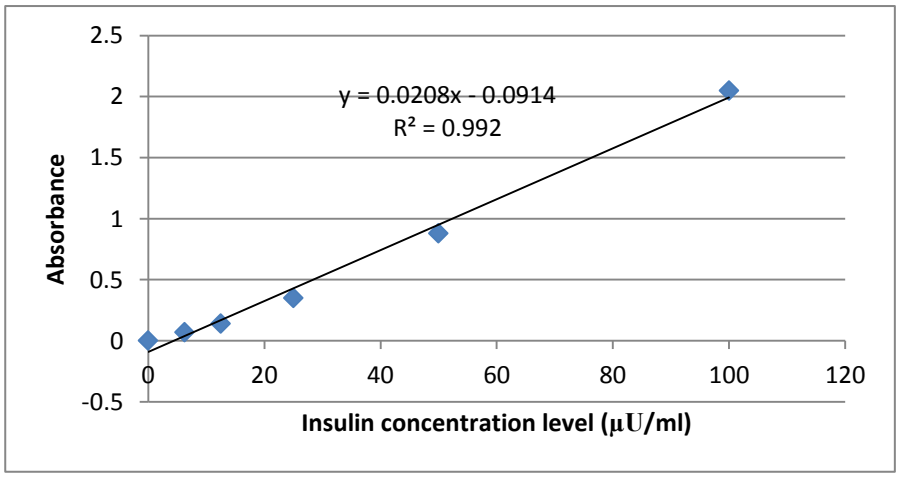


Figure 3: Standard curve of insulin.

RESULTS

Table 1 summarizes the demographic, metabolic, and hormonal parameters of the 90 T2DM patients (45 male and 45 female) after matching with 40 healthy control subjects for age, gender and BMI. Glycemic parameters for the patients group showed significant elevation as compared with the controls ($p<0.05$), FBS (174.32±56.89 vs. 88.21±25.63), HbA1c (8.65±2.23 vs. 5.27±0.61), FSI (29.25±8.68 vs. 14.05±6.27) and HOMA-IR (13.04±4.41 vs. 8.47±3.72).

TC and TG showed also an elevation while HDL-c showed a significant reduction for T2DM patients ($p<0.05$) as compared with the controls (215.06±38.61 vs. 154.15±45.34) (173.31±81.30 vs. 117.83±48.32) and (49.82±4.80 vs. 52.50±12.45) respectively. Leptin level showed an increase (21.68±5.86 vs. 18.70±0.60) and adiponectin showed a decrease (12.63±4.31 vs. 16.50±0.30) significantly in patients as compared to control group ($p<0.05$). LAR for diabetic patients was significantly higher ($p<0.01$) than non-diabetics (2.83 ± 1.35 vs. 1.24 ± 0.31).

Table 1: Characteristics of T2DM patients and control subjects

Characteristics	**T2DM group n=90**	**Control group n=40**	**P-value**
Age (years)	55.23 ± 4.52	42.41 ± 6.12	NS
Sex (M/F)	(45/45)	(20/20)	-
BMI (kg/m^2)	23.84 ± 4.45	22.97 ± 3.12	NS
FBS(mg/dl)	174.32 ± 56.89	88.21 ± 25.63	0.05
HbA1c %	8.65 ± 2.23	5.27 ± 0.61	0.05
FSI (µU/ml)	29.25 ± 8.68	14.05 ± 6.27	0.05
HOMA-IR	13.04 ± 4.41	8.47 ± 3.72	0.05
TC (mg/dl)	215.06 ± 38.61	154.15 ± 45.34	0.05
TG (mg/dl)	173.31 ± 81.30	117.83 ± 48.32	0.05
HDL-C (mg/dl)	49.82 ± 4.80	52.50 ± 12.45	0.05
Leptin (ng/ml)	21.68 ± 5.86	18.70 ± 0.60	0.05
Adiponectin (ng/ml)	12.63 ± 4.31	16.50 ± 0.30	0.05
LAR	2.83 ± 1.35	1.24 ± 0.31	0.01

Data are given as mean ± SD; n= number; NS= non-significant

Table 2 shows that leptin concentration was significantly lower as well as adiponectin concentration was significantly higher ($p<0.05$) in T2DM patients treated with metformin alone (group I) when compared to those treated with glibenclamide alone (group II) or those treated with metformin plus glibenclamide (group III), while non-significant difference was noticed between group II and group III.

Table 2: Leptin and Adiponectin level among different treatment groups

Variables/ Treatment Groups	**Group I n=30**	**Group II n=30**	**Group III n=30**
Leptin (ng/ml)	17.78 ± 3.76[a]	26.63 ± 6.21[b]	21.19 ± 7.61[b]
Adiponectin (ng/ml)	17.11 ± 4.40[b]	9.19 ± 3.21[a]	11.60 ± 5.32[b]

n=number; Data are given as mean±SD; Values with non-identical superscripts (a,b) among different groups are considered significantly different $p<0.01$.

Group I patients treated with metformin alone;

Group II patients treated with glibenclamide alone;

Group III patients treated with metformin+ glibenclamide.

HOMA-IR in group I and III (patients treated with metformin as monotherapy or combination) showed a significant positive correlation with leptin and negative correlation with adiponectin ($p<0.01$), but non-significant correlation was recorded in group II (patients treated with glibenclamide alone). Correlation of HOMA-IR with LAR found to be significant in metformin treated groups ($p<0.01$) while non-significant with glibenclamide group, as shown in table 3.

Figure 4 demonstrates a comparison for leptin and adiponectin concentrations between male and femaleT2DMpatients.

Table 3: Correlations between adipose secreted hormones; leptin and adiponectin; and their ratio (LAR) with HOMA-IR in T2DM patients

Variables / Groups	r and p values	HOMA-IR		
		Group I	Group II	Group III
Leptin	r	+0.86	+0.48	+0.85
	p	0.01	NS	0.01
Adiponectin	r	-0.92	-0.39	-0.90
	p	0.01	NS	0.01
LAR	r	+0.34	+0.41	+0.59
	p	0.01	NS	0.01

r=Pearson correlation coefficient; p-value<0.01 were considered statistically significant; NS non-significance
Group I patients treated with metformin alone;
Group II patients treated with glibenclamide alone;
Group III patients treated with metformin+ glibenclamide.

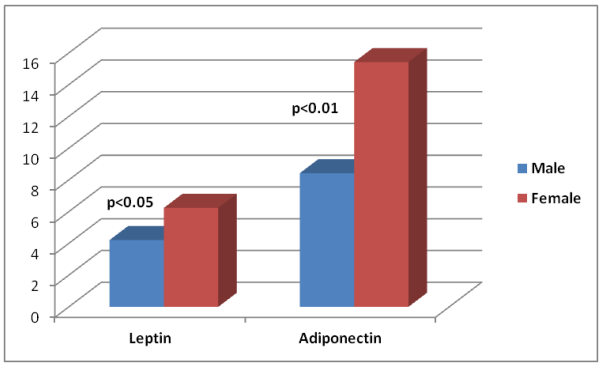


Figure 4: Comparison of leptin and adiponectin levels between male and female T2DM patients

DISCUSSION

After matching for BMI between diabetic and non-diabetic subjects, our results are consistent with previous studies, serum leptin level and LAR were higher in diabetics,[17,18,19] while serum adiponectin level was low compared with non-diabetics.[20] As most studies related the elevation of LAR to obesity, our study put a light on the elevated LAR in non-obese T2DM. These observations together along with increase in insulin resistance suggest that LAR can serve as index of insulin resistance, as well as in clinical practice, a good indicator for assessing the effectiveness of antidiabetic therapy.[21,22]

The evidence that insulin may have direct effect on leptin and adiponectin gene expression and their concentrations in vitro can explain the increase in leptin and decrease in adiponectin levels in our T2DM patients,[23,24] since high level of insulin combined with insulin resistance may cause an imbalance in the level of these adipokines. These findings are in accordance with other previous researches.[25] Furthermore, a study stated that the degree of hypoadiponectinemia is

more closely related to the degree of insulin resistance and hyperinsulinaemia than the degree of adiposity,[26] and other one stated that serum insulin concentration was correlated positively with serum leptin and negatively with serum adiponectin.[27]

Given these considerations, glibenclamide-treated group was the highest in leptin level and the lowest in adiponectin level supported by other studies investigated the effect of glibenclamide on leptin,[28,29,30] and on adiponectin,[31,32] levels in T2DM. Insulin stimulation effect of sulfonylurea can explain such effects. In contrast, metformin-treated group was the lowest in leptin level and the highest in adiponectin level supported by other studies.[33,34]

Our results agree with Fadil TA et al., leptin showed significant positive correlation with index of insulin resistance in both metformin and combination-treated groups, while no correlation was observed in glibenclamide-treated group.[35] These differences can be related to the insulin sensitization effect of metformin while glibenclamide as secretogogue agent have no effect on insulin resistance. Kadhim KA et al. reported such correlation only in large doses of metformin.[36] In contrast, adiponectin showed inverse correlation with insulin resistance in the same groups; metformin and combination; supported by other studies,[37,38] and also no correlation was observed in glibenclamide-treated group.

LAR also correlated positively with HOMA-insulin resistance index in metformin and combination-treated groups, this is compatible with the findings of Al-Hamodi Z et al. who stated that LAR is associated positively with leptin and negatively with adiponectin.[39]

Present study demonstrated a difference in serum leptin and adiponectin levels between genders. Women showed remarkably higher leptin concentration in agreement with other studies,[40,41] this may be attributed to a higher fat content in women which is main source of leptin or may be related to estrogens which can be another cause of high concentration of this hormone in women.[42] In contrast, women have higher adiponectin level than men because physiologically men have more visceral fat but women have more subcutaneous fat in which adiponectin is synthesized mainly.[43,44]

In conclusion, in T2DM patients LAR can serve as index of insulin resistance independent of BMI. LAR can measure the usefulness of antidiabetic therapy based on insulin level and insulin sensitivity.

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