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The Relation between Hypoadiponectinemia and Atherogenic Lipid Profile in Type2 Diabetic Males

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Abstract: *Adiponectin is an adipose tissue-derived adipocytokine which appears in diminished concentrations in a number of processes linked to cardiovascular disease, such as type2 diabetes. The aim of this study was to investigate the relationship between adiponectin, lipid profile, and atherogenic index in type2 diabetic patients.This study enrolled 60 type2 diabetic male subjects attend to the National Diabetic Center (Al-Mustansiyriyah University) Baghdad, Iraq; and 30 subjects serves as a control group. Fasting plasma glucose FPG, glycated hemoglobin HbA1c, insulin, lipid profile, and serum adiponectin were measured in T2DM males. Low density lipoprotein (LDL), atherogenic index and HOMA IR were calculated. Results showed that there was no significant difference for concerning waist circumference, systolic and diastolic blood pressure between the diabetic subjects and control subjects. Diabetic group showed a highly significant increase in FPG, HbA1c, lipid profile (TC, TG, LDL), and atherogenic index as compared with the control group. On the other hand, there was a significant decreased in serum adiponectin, and HDL-cholesterol in diabetic patients compared to healthy control. Adiponectin level was negatively correlated with BMI, systolic blood pressure, diastolic blood pressure, FPG, HbA1c, insulin, HOMA-IR, total cholesterol, triglycerides, LDL-cholesterol, and atherogenic index (AI); but it was positively correlated with HDL. Multiple linear regression analyses with adiponectin as the dependent variable with other variables as independent was executed with independent variable insulin, HOMA-IR, triglyceride, HDL-cholesterol, LDL-cholesterol, and atherogenic index (AI) were the significant establish even after adjustment for BMI. Although, FPG, and HbA1c, blood pressure tended to be negatively correlated with the serum adiponectin level, but did not reach statistical significance. Thus, the effects of adiponectin on FPG, HbA1c, and blood pressure are thought to be indirect, because the correlations with these parameters were not significant after adjustment for age and BMI .In conclusions, the current study supports the hypothesis that augmented adiponectin levels might be related with improved lipid profile in Type2 diabetic subjects. Thus, improving adiponectin levels might be precious goals for diminishing the atherosclerotic risk present in diabetes.*

Keywords: *adiponectin, lipid profile, type 2 diabetes.*

I. Introduction

Adipose tissue is regarded as to be not just a simple reservoir of energy but also an organ which is dynamically involved in metabolic control by secreting adipocytokines which play important biological roles[1]. One of these adipose tissue-derived adipocytokines, adiponectin, is responsible for rising energy expenditure and lipid catabolism as well as enhancing fatty acid oxidation and insulin sensitivity[2]. Decrease adiponectin concentrations are inversely associated with insulin resistance[3], are predictive of type 2 diabetes onset[4].Patients with type 2 diabetes have a markedly increased atherosclerotic risk. The risk of fatal coronary heart disease among diabetic subjects is comparable with that observed in subjects who have had a previous myocardial infarction[5,6]. This increased risk has been mainly attributed to hyperglycemia, dyslipidemia, and inflammatory mechanisms[7]. Adiponectin, which is solely synthesized in the adipose tissue, appears to play an important role in all of these pathways[3].

Adiponectin is considered to be a defensive factor in the pathogenesis of a number of processes associated to cardiovascular disease[8,9]. Plasma adiponectin concentrations are also positively associated with favorable plasma lipid profiles and decreased concentrations of inflammatory markers, suggesting that adiponectin may affect cardiovascular disease by modulation of plasma lipids and low-grade, chronic inflammation[10]. In recent years, adiponectin has been reported to possess various physiological activities. Adiponectin has been associated with dyslipidemia in type 2 diabetes mellitus [11]. An inverse correlation has been shown with triglycerides levels and low-density lipoprotein (LDL) and a positive correlation with high-density lipoprotein (HDL) cholesterol.[12] As well as, some evidence suggests that low adiponectin plasma concentrations are associated with high concentrations of HDL cholesterol (HDL-c)4 and low concentrations of triglycerides[13-16]. In contrast, reported data on the relationship of adiponectin to apolipoprotein (apo) B100 and LDL cholesterol (LDL-c) have been inconsistent[15,16].

The current study scrutinized the relationship between serum adiponectin lipid profile, and atherogenic index in a group of Iraqi type2 diabetic subjects. The aim of the present study was to investigate adiponectin,

and serum lipoprotein lipid concentrations in type 2 diabetic subjects. In addition, it was of particular interest to explore the relationships between adiponectin, serum lipid, athrogenic index, and different clinical and demographic characteristics of type 2 diabetic men. Moreover, because sex difference had been reported in serum adiponectin, serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), the present study chose men only.

II. Subjects And Methods

The current study included 60 males who were previously diagnosed type2 diabetic patients attend to the National Diabetic Center (Al-Mustansiyriah University) Baghdad, Iraq. And 30 healthy males severs as a control group.Diabetic and control groups were confirmed to have no known disease (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 meals or with sulphonylurea an oral hypoglycaemic agent. Patients being treated with insulin were excluded.

All patients and control subjects that had a body mass index >30 kg/m^2 were excluded from the study. A full medical history, including age, sex, diabetic duration, and treatment were recorded on all patients and control subjects. A clinical examination, including weight, height, as well as laboratory measures was completed. All subjects were matched with 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 -20 ^{0}C, and were analyzed at later time for insulin, Adiponectin, and leptin. Laboratory evaluations consisted of measuring glycemic control including (fasting plasma glucose (FPG), glycated hemoglobin HbA_{1c}), lipid profile [total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), and low density lipoprotein (LDL)] were measured immediatly.

Hemoglobin A_{1c} program intended for the determination of Glycated hemoglobin ($A1_c$) 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, and High density lipoprotein (HDL) were determined using kits from (biomaghreb, Sa, France). Low density lipoprotein (LDL) was calculated mathematically using the Friedwald formula; and the atherogenic index was calculated by using the formula: AI= log (TG/HDL-C)[17].Adiponectin(A) assay: done by the human adiponectin ELISA kit is used for non–radioactive quantification of human adiponectin. This kit (DRG, USA) specifically measures native human adiponectin and has no cross reactivity to mouse 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][18].

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 adiponectin after adjustment for confounding variables.

III. Result

The current study showed that there was no significant difference for age and BMI between the diabetic subjects and control subjects. Also concerning waist circumference, systolic and diastolic blood pressure, there were no significant differences between the two groups. The type2 diabetic group showed a highly significant increase in fasting blood glucose, glycated hemoglobin A1c, lipid profile (TC, TG, LDL), and atherogenic index(175.1± 17.84 vs 96.23±16.18 $p<0.01$; 8.89 ± 2.56 vs 5.89 ±0.94, $p<0.01$; 223.6 ± 18.76 vs 165.14± 16.44, $p<0.01$; 180.77 ±16.7 vs 120.88 ±13.34, $p<0.01$; 124.5±23.35 vs 100.3± 19.24, $P<0.05$; and 4.57 ± 1.04 vs 2.09 ± 0.28, $p<0.05$) respectively, as compared with the healthy control group as shown in (Table 1). On the other hand, there was a significant decreased in serum adiponectin, and HDL-cholesterol in diabetic patients compared to healthy control (8.05 ± 2.77 vs 14.98 ± 3.92, $p<0.01$; and 38.64 ±7.43 vs 40.89 ± 8.35, $p<0.05$) respectively. Moreover, there was a highly significant increase in the serum insulin and insulin resistance

[HOMA-IR] in diabetic patients compared to healthy control (14.32 ± 3.87 vs 8.83 ± 2.1; 5.99 ±1.02 vs 2.01 ± 0.07, p<0.01) respectively.

Another finding in the current study showed that the serum adiponectin level was negatively correlated with BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HbA1c, insulin, HOMA-IR, total cholesterol, triglycerides, LDL-cholesterol, and atherogenic index (AI) (r=-0.485, P<0.01; -0.245, P<0.05; -0.221, p<0.05; -0.278, P<0.05; -0.291, p<0.05; -0.250, p<0.05; -0.401, P<0.01; -0.266, p<0.05; -0.589, p<0.01, -0.328, p<0.01; and -0.369, p<0.01) respectively. On the other hand adiponectin was positively correlated with HDL-cholesterol (r= 0.431, p<0.01) as shown in (Table2).

Moreover, Table 3 showed multiple linear regression analyses with adiponectin as the dependent variable with other variables as independent. When the analysis was executed with independent variable insulin, HOMA-IR, triglyceride, HDL-cholesterol, LDL-cholesterol, and atherogenic index (AI) were the significant establish even after adjustment for BMI, as shown in table3. Although, the fasting serum glucose, and HbA1c, blood pressure tended to be negatively correlated with the serum adiponectin level, but did not reach statistical significance. Thus, the effects of adiponectin on fasting serum glucose, HbA1c, and blood pressure are thought to be indirect, because the correlations with these parameters were not significant after adjustment for age and BMI.

IV. Discussion

The results of this study revealed significantly greater levels of total cholesterol and triglycerides in group type 2 diabetic males as compared with normal control subjects. Hypertriglyceridemia is identified metabolic correlate of hyperinsulinemia, insulin resistance, and glucose intolerance; the current study showed the presence of insulin resistance in patients' group[19]. Moreover the present study demonstrated a significant decrease of the serum adiponectin levels in the diabetic patients compared to healthy control group. Reduced adiponectin is linked to impaired insulin action in type 2 diabeticts.[20] Adiponectin concentration was significantly associated with insulin sensitivity.[20]

Moreover, the results showed that adiponectin was positively correlated with HDL-cholesterol which revealed that low levels of adiponectin in diabetic males are associated with low levels of HDL cholesterol and might be an independent cardiovascular risk factor, whereas high levels of adiponectin are associated with high levels of HDL cholesterol, indicating a protective profile. In addition, this result may be analogous with the antiatherogenic properties of adiponectin. Thus, considering the mechanism standing behind the observed relations might give the basis for the development of ''adiponectin agonist'' as HDL-enhancing drug. The mechanisms by which adiponectin may affect HDL cholesterol levels are largely unknown. Effects of adiponectin on hepatic lipase activity, which is augmented in central obesity and insulin resistance, are supposed[15]. However, relations between adiponectin and HDL cholesterol seem to be generally independent of body fat[12,14,15,21-24] and insulin resistance[22-24]. This proposed that mechanisms other than effects on insulin resistance and hepatic lipase activity most likely mediate the relationship between adiponectin and HDL cholesterol and that this relationship is only in part a mediation of metabolic effects of body fat. Adiponectin induces AMP-activated protein kinase[25,26], resulting in the motivation of glucose uptake in muscle; fatty acid oxidation in muscle and liver; and the inhibition of hepatic glucose production, cholesterol and triglyceride synthesis, and lipogenesis. Adiponectin therefore may reduce tissue fatty acid content and serum lipids. As a secondary effect of low adiponectin levels, the raise in HDL core triglyceride content that occurs as a result of increased neutral lipid exchange between triglyceride-rich lipoproteins and HDL in hypertriglyceridemic, insulin resistant states may lead to a decline in HDL particle numbers and cholesterol content, potentially by predisposing HDL particles to improved catabolism[27].

The present results demonstrating that serum adiponectin concentrations are not only inversely correlated to total cholesterol, triglycerides, and atherogenic index, but also positively correlated to serum HDL-cholesterol. We also found that the serum adiponectin concentration before and after adjustment for BMI was negatively correlated with triglycerides, atherogenic index, and positively with HDL-C. Because adiponectin acts to diminish atherogenic reaction[28-31], these data have been interpreted to show that hypoadiponectinemia in dyslipidemia accelerates the atherogenic reaction. The mechanism underlying the observed close association between plasma adiponectin and dyslipidemia is presently unknown. As, we explained this may be attributeable to insulin resistance and/or hyperinsulinemia[23,33]. Yamauchi *et al.*[33] reported that adiponectin administration leads to diminished muscle and liver TG content, increasing combustion of FFA in obese and diabetic mice. Therefore, adiponectin reverses insulin resistance in obese and diabetic mice[33]. Recent genomic scan studies[34,35] have revealed association of the metabolic syndrome and/or diabetes to a region on chromosome 3 (3q26 –27), where the gene encoding adiponectin, apM1, is located[36].

Adiponectin is a plasma protein that is secreted specifically by adipocytes, and its function as an anti-atherosclerotic factor is being elucidated[28-30]. The present study revealed interaction between adiponectin and insulin resistance index, lipids and blood pressure, which are important risk factors for the development of

atherosclerosis. The serum adiponectin level was negatively correlated with insulin resistance (HOMA-IR) in diabetic males, even after adjustment for age and BMI. As for lipid profiles, persons with a higher adiponectin level had lower LDL-cholesterol, lower triglycerides and elevated HDL-cholesterol. Because both adiponectin and lipids were correlated with BMI, the current study result adjusted for age and BMI, but the correlations between lipids and adiponectin were still significant. The results of this study indicate that adiponectin is related to insulin resistance index and lipid profile, independent of age and BMI, whereas the effects of adiponectin on blood pressure are thought to be indirect, because the correlations with these parameters were not significant after adjustment for age and BMI.

The correlation coefficient showed that, when the adiponectin level is high, insulin resistance is low and the lipid profile is good. It is unclear, whether adiponectin improves both insulin resistance and lipid profile, or whether decrease insulin resistance and or a good lipid profile augment the serum adiponectin level. Animal studies have revealed that acute treatment of mice with the globular head domain of Acrp30, the mouse counterpart of adiponectin, significantly decreased plasma glucose, non-esterified fatty acid and triacylglycerol levels through an acute increase in fatty acid oxidation by muscle[37]. In a study of Pima Indians, Weyer et al.[32] reported that the plasma adiponectin level was positively correlated with insulin sensitivity. However, they did not prove the association between adiponectin and lipids. Some research[38,39] have shown recently that administration of thiazolidinediones increases plasma adiponectin levels in diabetic subjects. Furthermore, a genome scan in French Caucasians presented strong data for a susceptibility locus for diabetes and impaired glucose tolerance on chromosome 3q27[35], where the adiponectin gene (*apM1*) is located. Also, pedigree-based analysis using a variance components linkage model demonstrated a quantitative trait locus on chromosome 3q27 that is strongly linked to the metabolic syndrome[34]. When these and more recent reports[33,40] are taken into consideration, the possibility that adiponectin improves insulin resistance and lipid profile seems more likely.

In conclusion, the current study demonstrated that adiponectin was significantly associated with lipid concentration and atherogenic index before and after adjustment for body mass index. Thus, these findings suggest that high adiponectin levels may be a superior independent predictor of the atherogenic lipid profile, and may have a protective effect on atherosclerosis in type2 diabetic males.

Table1: the general characteristics of patients and control

	G1:Patients	**G2:Control**
No.	60	40
Age, yrs	47.9±12.28	47.3 ±13.01
BMI (kg/m^2)	25.02±4.63	25.08 ±2.78
WC (cm)	97 ± 3.3	102 ± 3.1
SBP (mmHg)	129.3±16.1	125 ± 16.79
DBP (mmHg)	77.3 ± 10.5	72.3 ± 10.01
FPG (mg/dl)	175.1± 17.84**	96.23±16.18
$HbA1_c$	8.89 ± 2.56**	5.89 ±0.94
TC (mg/dl)	223.6 ± 18.76**	165.14± 16.44
TG (mg/dl)	180.77 ±16.7**	120.88 ±13.34
HDL-C (mg/dl)	38.64 ±7.43*	40.89 ± 8.35
LDL-C (mg/dl)	124.5±23.35*	100.3± 19.24
Insulin (µIU/ml)	14.32 ± 3.87**	8.83 ± 2.11
HOMA-IR	5.99 ±1.02**	2.01 ± 0.07
Adiponectin (ng/ml)	8.05 ± 2.77**	14.98 ± 3.92
Atherogeic index	4.57 ± 1.04*	2.09 ± 0.28

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

Table 2: Correlation analysis between Adiponectin, and variables in patients.

	Adiponectin
	R
Age	+0.101
BMI	-0.485**
WC	-0.185
SBP	-0.245*
DBP	-0.221*
FSG	-0.278*
$HbA1_c$	-0.291*
TC	-0.266*
TG	-0.589**
HDL-C	0.431**
LDL-C	-0.328**
AI	-0.369**
Insulin	-0.250*
HOMA-IR	-0.401**

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

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

Table3. Multiple linear regression analysis with Adiponectin as the dependent variable including the some variable as independent.

Independent variable	Adiponectin
	Beta
FSG	-0.091
HbA1c	-0.018
TG	-0.799**
TC	0.023
HDL	0.512**
LDL	0.299*
AI	0.412**
Insulin	-0.289*
HOMA-IR	-0.297*
R2	0.623

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

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