Association of Serum Adipokines Levels with Glycemic Control and Metabolic Dyslipidemia in Sudanese Patients with Type 2 Diabetes Mellitus

Halima Babiikir Eltahir (✉ halimaeltahir@hotmail.com)

Ahfad University for Women School of Medicine <https://orcid.org/0000-0002-7645-4960>

Elmahdi Mohamed Ali

University of Khartoum Faculty of Medicine, department of internal medicine

Abdelrahim Osman Mohamed

university of khartoum, faculty of medicine, department of biochemistry

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Abstract

Background: The pathogenesis of type 2 diabetes mellitus is due to two major abnormalities including insulin resistance and dysfunction, which lead to the inability to regulate blood glucose level. Adiponectin is a hormone secreted by the adipose tissue and it takes part in glucose metabolism with insulin-sensitising properties. Low levels of adiponectin leads to reduction of fatty acid oxidation decreased glucose uptake in skeletal muscle cells and increased level of free fatty acids leading to insulin resistance. Leptin is another adipokine produced by adipose tissue involved in the control of food intake via its action on the hypothalamus, suppressing appetite and stimulating energy expenditure. Leptin plays a critical role in pathophysiology of type 2 diabetes mellitus.

The aim of the study was to investigate the association of serum adipokines levels with glycemic control and metabolic dyslipidemia in Sudanese patients with type 2 diabetes mellitus.

Methods: This was a case control study. 202 patients with type 2 diabetes and 102 non-diabetic controls participated after signing written consent. Weight (kg) and height (m) were measured then the body mass index (kg/m²) was determined. Blood samples were collected after an overnight fasting. FBG, HbA1c and lipid profiles were measured using enzymatic methods. Adiponectin and leptin were measured using sandwich ELISA.

Results: Adiponectin concentrations was significantly lower in patients with type 2 diabetes compared with the controls ($p < 0.001$) and it was inversely correlated with HbA1c (Pearson Correlation -0.160 , P value $= 0.005$), total cholesterol and LDL levels ($P = 0.05$) and direct correlated HDL levels ($P = 0.05$). Leptin concentrations was significantly higher in patients with type 2 diabetes compared with the controls ($p < 0.002$) and it was positively correlated with HbA1c (Pearson Correlation 0.155 , P value $= 0.02$), total cholesterol and LDL levels ($P = 0.05$), there were no correlation with HDL and TG levels. Patients had significantly higher fasting blood glucose, HbA1c levels, total cholesterol and LDL levels compared with the controls.

Conclusion: Patients with type 2 diabetes mellitus had decreased levels of serum adiponectin, high levels of serum leptin. There were significant correlations found between adiponectin and leptin levels with glycemic control and metabolic dyslipidemia .

Background

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia as a result of pancreatic B-cell dysfunction and insulin resistance [1]. The number of adults with diabetes mellitus has been increasing annually, it is expected that more than 640 million adults will have diabetes by 2040 [2]. DM occurs throughout the world but is more common (especially type 2) in more developing countries. The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will probably be found by 2030 [3]. In 2011 WHO estimated that in the African region 14.7 million adults was living with diabetes mellitus, the African Region is expected to have the largest proportional increase

of all of WHO's regions (90.5%) in the number of adult diabetics by 2030 [4]. DM has a high risk of disabilities, decrease in quality of life due to a serious medical problem that causes many serious complications such as diabetic neuropathy, retinopathy, nephropathy and atherosclerotic vascular disease [5]. DM is a major cause of death in most countries, it accounts for 5.1 million deaths worldwide every year [6]. The diagnosis of diabetes mellitus is clinical and is based on multiple measurements of blood glucose; it is generally classified into two main types (1 and 2), with type 2 DM accounting for more than 90–95% of the cases [7].

Type 2 diabetes mellitus constitutes up to 95% of all diabetes, with prevalence of 1.2% in developed countries, whereas in developing countries the prevalence is assumed to be fourfold higher [8, 9]. Type 2 diabetes mellitus is characterized by chronic hyperglycemia resulting from defects in insulin secretion and/or insulin action and metabolic disorders of protein and lipids [10, 11]. The pathogenesis of type 2 diabetes mellitus is due to two major abnormalities including insulin resistance and dysfunction of insulin production, which lead to the inability to regulate blood glucose level [12], resulting in insufficient production of adiponectin and increased production of pro-inflammatory cytokines as a result of the major contributing factors to type 2 diabetes mellitus such as obesity, dyslipidemia, hypertension and other metabolic disorders. [13, 14, 15].

Adipose tissue, in addition to being a fat store, secretes a number of hormones and proteins collectively termed adipokines [16]. Adiponectin is a 244–amino acid collagen-like protein mainly produced in adipocytes, its production can sometimes occur or be up-regulated in other tissues such as the liver, skeletal muscle, and cardiac muscle especially in the presence of inflammation [17, 18]. It acts as a hormone with anti-inflammatory and insulin sensitizing properties as well as its role in glucose metabolism [19, 20]. Animal studies and metabolic studies in humans have shown that adiponectin improves insulin sensitivity and decreases the risk of type 2 diabetes through several mechanisms including suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of fatty acid oxidation and glucose uptake in skeletal muscle, and stimulation of insulin secretion [19, 21].

Adiponectin is encoded by the adipose most abundant gene transcript 1 (*APM1*) located on chromosome 3q27 [22]. This gene is abundantly expressed in adipocytes and circulates in the blood at high concentrations, which is among the highest plasma concentrations of a circulating protein.(ref) In humans, adiponectin plasma levels range from 3 to 30 µg/mL [23]. Plasma adiponectin levels decrease in parallel with the progression of insulin resistance, suggesting that a reduction in circulating adiponectin may be related to the development of insulin resistance [24, 25]. Serum adiponectin concentrations are reported to decrease in patients with Type 2 diabetes mellitus, obesity and coronary heart disease [26]. Adiponectin exerts its effects by binding to two receptors, AdipoR1 and AdipoR2. AdipoR1 and AdipoR2 regulate metabolic gene expression and insulin sensitivity in insulin target tissues, and are important in the pathophysiology of insulin resistance and diabetes [27, 28, 29]. Insulin resistance leads to down regulation of adiponectin receptors in muscle and liver [30].

Leptin is the product of the *obese* gene (*ob*), is an adipokine produced by adipose tissue involved in the control of food intake through its action on the hypothalamus[31]. Leptin action leads to suppression of appetite, regulation of body weight by inhibiting food intake and stimulating energy expenditure [31]. Leptin plays a critical role in regulation of blood glucose by having positive interaction with insulin. Leptin is linked with body fat percentage, BMI, and insulin concentration [32]. Leptin receptors are present in the hypothalamus and in tissues regulating glucose homeostasis, including skeletal muscle, liver, pancreas, and adipose tissue [33]. Leptin has been shown to stimulate glucose uptake and fatty acid oxidation in skeletal muscle, prevent lipid accumulation in non-adipose tissues such as skeletal muscle, liver, and pancreatic B cells and to inhibit insulin secretion through leptin receptors on pancreatic B-cells [34]. Leptin is involved in pathways influencing the risk of cardiovascular disease, insulin resistance and type 2 diabetes mellitus [35]. Patients with type 2 diabetes have a remarkably increased risk of cardiovascular diseases. This increased risk has been mainly attributed to hyperglycemia, dyslipidemia and inflammatory mechanisms [36]. Dyslipidemia is a broad term used to define various lipid disorders; from hyperlipidemia to hyperlipidemia, it is a major risk factor of vascular complications in patients with type 2 DM [37], dyslipidemia includes higher low-density lipoprotein cholesterol (LDL), hypertriglyceridemia (TG), low high-density lipoprotein cholesterol (HDL), and mixed lipid disorder[38]. Recently Metabolic Dyslipidemia” is commonly being used to reflect abnormal lipid pattern dominant in patients with type 2 DM [39]. Adipose tissue plays a major role in pathogenesis of dyslipidemia, several studies have demonstrated that impaired adipokines secretion causing inflammation in adipose tissue, can lead to dyslipidemia [40].

The aim of the study was to investigate the association of serum adipokines levels with glycemic control and metabolic dyslipidemia in Sudanese patients with type 2 diabetes mellitus.

Materials And Methods:

This was a case- control study conducted at Jabir Abu Eliz Diabetic center in Khartoum, Sudan. Two hundred and two patients with type 2 diabetes mellitus aged 40–59 years, diagnosed according to the criteria of the WHO FBG ≥ 126 mg/dL (7.0 mmol/L) and who attended the diabetes clinic on Sundays and Tuesdays during the study period between February and December 2014 were included in the study after signing written consent. One hundred and two age matched healthy volunteers were included as controls. The controls had normal FBG < 110 mg/dl (< 7.0 mmol/l). This study was approved by the ethical committee of the board of medical and health sciences, University of Khartoum and the ethical committee of the state of Khartoum ministry of health.

All participants were interviewed with a questionnaire to collect data including age, sex, duration of the disease and information related to diagnosis and follow up. Clinical examination was performed.

Blood sampling:

Blood samples were collected from all subjects in the morning after 6–8 hours overnight fast using EDTA, Sodium fluoride and plain containers and were processed as follows; EDTA blood samples were used for HbA1c analysis during the same day. Then plasma and serum were separated with centrifugation and were immediately stored at – 80 °C for subsequent assay.

Laboratory analyses:

Fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels were measured using enzymatic colorimetric methods. Glycosylated hemoglobin % (HbA1c %) was measured using boronate-affinity binding enzymatic methods using Nycocard HbA1c (Axis-shieldPoC AS, Oslo, Norway) [41]. Sandwich ELISA was used for estimation of serum adiponectin and leptin levels by using commercial ELISA Kits.

Statistical analysis:

SPSS statistics (V.20.0, IBM Corp., USA, 2010) was used for analysis of data. Students t -test for independent variables was used for comparison of means. Pearson correlation and scatter plots were used to evaluate bivariate relationships between HbA1c, adiponectin and leptin levels in the patients $P < 0.05$ was considered significant.

Results:

The study included 202 patients with type 2 diabetes mellitus and 102 healthy controls. Anthropometric and biochemical variables of the studied subjects are presented in Tables 1 and 2. There was no significant difference between means of age (51.9 years) for patients and controls (51.02 years) P -value > 0.05 . Systolic and diastolic blood pressure were significantly higher among patients with type 2 DM compared with controls ($P < 0.001$), the biochemical variables (FBG, HbA1c, TC, LDL) were significantly higher among patients compared with controls ($P < 0.001$), High density lipoprotein (HDL) was significantly lower in patients ($P = 0.001$). BMI and triglycerides (TAG) differences between the groups were not significant. Patients had significantly lower serum adiponectin and higher leptin levels compared with the controls ($P = 0.001$, $p = 0.002$ respectively) (Table 1).

There was no significant difference in means of adiponectin and leptin in regard to gender distribution ($P > 0.05$). (Table 2).

Among the patients, adiponectin level showed significant inverse correlations with HbA1c ($P = 0.01$), total cholesterol and LDL levels ($P = 0.05$). In the control subjects, adiponectin level did not show any significant correlations with all biochemical parameters. NO significant correlation was found between adiponectin and BMI in both Patients and controls (Table 3).

Leptin had significant positive correlations with HbA1c, Total cholesterol and LDL levels ($P = 0.05$), there were no correlation with HDL and TG levels. There was no significant correlation found between leptin and BMI in both Patients and controls (Table 3).

Table (1) Anthropometric and biochemical variables of patients with type 2 diabetes mellitus and controls

Variable	Patients	Controls	P-Value
	Mean $\pm$ S.D (n = 202)	Mean $\pm$ S.D (n = 102)	
Age (years)	51.91 $\pm$ 4.19	51.02 $\pm$ 4.31	0.084
SBP (mmHg)	130.6 $\pm$ 8.79	120.5 $\pm$ 5.98	0.000
DBP (mmHg)	87.0 $\pm$ 6.68	80.3 $\pm$ 3.36	0.000
BMI (kg/m ²)	25.80 $\pm$ 3.65	24.60 $\pm$ 4.81	0.01
FBG (mg/dl)	180.81 $\pm$ 47.15	100.06 $\pm$ 13.18	0.000
HbA1c (%)	8.77 $\pm$ 2.36	5.09 $\pm$.696	0.000
Adiponectin	16.98 $\pm$ 10.41	21.95 $\pm$ 13.85	0.001
Leptin	17.78 $\pm$ 4.61	15.96 $\pm$ 4.93	0.002
T C (mg/dl)	178.67 $\pm$ 33.54	142.11 $\pm$ 31.05	0.000
LDL (mg/dl)	86.28 $\pm$ 24.030	62.77 $\pm$ 17.36	0.000
HDL (mg/dl)	48.52 $\pm$ 14.29	54.27 $\pm$ 14.81	0.001
TG (mg/dl)	120.89 $\pm$ 29.97	119.62 $\pm$ 32.20	0.733

SBP (mmHg) systolic blood pressure; DBP(mmHg) diastolic blood pressure; BMI (Body Mass Index); FBS (Fasting Blood Sugar); HbA1c (Haemoglobin A1c); TC (Total cholesterol); TG (Triglycerides); HDL (High Density Lipoproteins); LDL (Low Density Lipoproteins)

Table (2) Adiponectin and leptin levels among male and female patients with type 2 diabetes mellitus

Variable	male Patients No 95	Female patients No 107	P-Value
	Mean $\pm$ S.D (n = 202)	Mean $\pm$ S.D (n = 102)	
Adiponectin	17.8682 $\pm$ 10.66485	16.1922 $\pm$ 10.16784	.255
Leptin	18.0177 $\pm$ 4.13943	17.5667 $\pm$ 5.00749	.489

Table (3): Correlations of adiponectin with BMI, HbA1c and lipid profiles in patients and control

Adiponectin level				
Patients (n = 202)			Controls (n = 102)	
	Pearson Correlation	P-value	Pearson Correlation	P-value
BMI (kg/m2)	.080	.260	.99	.330
HbA1c (%)	– .197**	.005	.056	.577
T C (mg/dl)	.139*	.049	– .110	.275
LDL (mg/dl)	.161*	.022	.034	.736
HDL (mg/dl)	.157*	.025	.088	.386
TG (mg/dl)	.004	.950	– .130	.199
**P value < 0.01 (2-tailed).				
*P value < 0.05 (2-tailed).				

Table (4): Correlations of Leptin levels with BMI, HbA1c and lipid profile in patients and control group

Leptin level				
Patients (n = 202)			Controls (n = 102)	
	Pearson Correlation	P-value	Pearson Correlation	P-value
BMI (kg/m2)	.035	.618	.068	.501
HbA1c (%)	.139*	.048	– .099	.329
T C (mg/dl)	.138*	.050	.102	.312
LDL (mg/dl)	.157*	.026	– .146	.148
HDL (mg/dl)	.020	.782	.137	.174
TG (mg/dl)	– .124	.080	.056	.577
*P value < 0.05(2-tailed).				

Discussion

This study assessed the association of serum adipokine and leptin levels with glycemic control and dyslipidemia in Sudanese patients with type 2 diabetes mellitus.

In this study, adiponectin levels were significantly lower among patients when compared with control group. The findings of the study agreed with previous studies suggesting that adiponectin may play a role in glucose metabolism and low adiponectin levels are frequently reported in type 2 diabetes in

different ethnic groups [42, 43]. Higher serum adiponectin levels were reported to be associated with lower risk of diabetes among Japanese, Mexicans, Asian Indians Kashmiri and other populations [44, 45, 46]. The low levels of adiponectin seen in diabetic patients are believed to be associated with the disorder of glucose and lipid metabolism [47,48], and this explains the presence of insulin resistance in type 2 DM patients. The explanation of the association between diabetes and adiponectin could be related to the anti-diabetic effects of adiponectin. Adiponectin has been reported to promote pancreatic beta-cell function, increase insulin sensitivity by stimulating hepatic insulin signaling by enhancing Insulin receptor substrate 2 expression [49]. Adiponectin also increases glucose uptake by stimulating the translocation of the glucose transporter 4 (GLUT4) to the cell surface [50]. Adiponectin has also been reported to modulates the interaction between hepatic and skeletal muscle insulin receptors by activation of 5 adenosine monophosphate-activated protein kinase (AMPK) pathway [51]. Other potential mechanisms of the glucose lowering effect of adiponectin include; suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of glucose uptake and fatty acid oxidation in skeletal muscle [52]. This result demonstrates a clear significant relationship between plasma adiponectin concentration and Type 2DM. Thus, adiponectin has increasingly been considered a potential biomarker for type 2DM.

In this study, adiponectin was inversely correlated with HbA1c levels similar to previous studies [53,54], indicating that adiponectin could be used as a marker for evaluation of glycemic control and disturbance of glucose metabolism in diabetic patients. The reduction of serum adiponectin in patients was independent of their body mass indices. In contrast with the previous studies that have shown adiponectin levels negatively correlated with BMI and insulin resistance in diabetic patients [55,56,57]. However, other previous reports agreed with this study that there was no correlation between adiponectin and BMI in diabetic patients [58,59]. It could be explained by the fact that adiponectin concentrations were mostly linked with insulin sensitivity rather than insulin resistance in type 2 diabetic patients.

Leptin levels were high in the patients with type 2 diabetes compared with controls, and positively correlated with HbA1c levels in the patients. This could explain the role of leptin in glucose homeostasis. The insulin sensitizing effects of leptin have been related to increased fatty acid oxidation and decreased triglyceride storage in muscle [60,61]. It has been identified as an important regulator of pancreatic b-cell mass and inhibition of insulin gene expression [62], mediation of direct inhibitory effects of leptin on insulin secretion may be disrupted under conditions of increased leptin levels such as type 2DM and obesity [62, 63].

The study results showed no significant difference in BMI between diabetic patients and healthy controls, in agreement with previous reports [64], serum leptin levels were not correlated with BMI in diabetic patients. In relation to this aspect, a previous study found an association between diabetes and leptin levels when BMI was adjusted in the regression model [65]. It is probable that factors other than increased body fat content also contribute to the elevated leptin levels in diabetic patients. There were some studies that have shown positive correlation between leptin and BMI in patients with type 2DM [66,

67]. In agreement with a previous study [68], serum adiponectin and leptin levels did not vary significantly between genders although significant differences were observed in patients and controls.

Adiponectin was found to be correlated with various parameters of lipids profile, it is especially associated with HDL and TG. Adiponectin induces an increase in serum HDL and, in addition, it lowers serum TG through the enhanced catabolism of TG-rich lipoproteins [69]. The findings of the current study showed that, serum lipid profile of type 2 diabetic patients was abnormal compared with those of the controls whose lipid profiles were mostly within normal values. This confirmed the well-known association of dyslipidemia with type 2 diabetes [70]. In this study the positive correlation between serum adiponectin and HDL levels in the patients, is in agreement with previous studies that reported positive correlation between HDL and adiponectin that was independent of BMI and insulin resistance in type 2 diabetic patients [71, 72, 73, 74]. It could be explained by the fact that decreased adiponectin levels have been related to increased hormone sensitive lipase activity, which may be responsible for the decreased levels of HDL cholesterol [75, 76]. Several studies have investigated the relationship between adiponectin, LDL and TC levels, but the results were controversial, previous studies showed that the level of adiponectin has an inverse relationship with LDL and TG [72, 73, 74], another study showed no significant correlation between serum adiponectin level, LDL cholesterol and total cholesterol in type 2 diabetic patients [77]. In the current study there were inverse correlations between serum adiponectin with LDL and TC in the patients, a similar study conducted in Japan showed a negative correlation between serum adiponectin levels and LDL, TC, levels in type 2 diabetics [78]. The negative correlation was explained to be due to low levels of adiponectin which is associated with reduced activation of peroxisome proliferator activator receptor-alpha (PPAR- α) receptors in the liver and decreased expression of LDL receptors in body tissues [78]. A Previous study reported inverse correlation between serum adiponectin and TG level in the type 2 diabetic patients [79].

It has been explained by the hypothesis that adiponectin may increase the production and activation of lipoprotein lipase and the expression of VLDL receptors by activation of PPAR in liver which will reduce the storage of triglycerides in adipose tissue and their uptake by the hepatocytes and increase concentration of triglyceride in the blood (hypertriglyceridemia) [80]. In contrast, this study showed there was no correlation between serum adiponectin and TG level in the type 2 diabetic patients.

The association between leptin and lipid metabolism has been reported in animal studies, leptin deficiency has been observed to be associated with hyperglycemia, hyperlipidemia, and insulin resistance [81]. There are contradictions between the relations of serum leptin levels and lipids profile. Some studies reported that there was no relationship between leptin and the parameters of a lipid profile [82, 83]. Other study showed a significant positive correlation between leptin and lipid profile (HDL, TG) [84].

In current study leptin levels seem to correlate only with selected lipid profile parameters (TC and LDL), in agreement with previous study the results showed positive correlation between leptin level and total cholesterol [85]. A study on Japanese showed that there was a significant relationship between serum leptin level and LDL in diabetic patients [86], these results are consistent with this study and another

study conducted showed a positive correlation between serum leptin level and LDL in white subjects [87]. Despite the link between serum leptin levels and lipid metabolism and the indication that high leptin levels are biomarkers of obesity [88], this study did not demonstrate a correlation between leptin level, TG and HDL, in agreement with a previous study [89].

Conclusion

Sudanese diabetic patients had decreased level of serum adiponectin and elevated levels of serum leptin. Serum adiponectin level is negatively associated with HbA1c and serum leptin level is positively associated with HbA1c, the present study supports that adipokines levels associated with glycemic control and incidence of dyslipidemia in type 2 diabetes.

Abbreviations

DM: diabetes mellitus; EDTA: Ethylene diamine tetra acetic acid; HbA1c: glycated Hemoglobin; BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; TAG: triacylglycerol; ELISA: enzyme linked immunosorbent assay.

Declarations

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Halima Babikir Eltahir (HBE) research design, patient recruitment and data collection, laboratory analysis, data analysis, manuscript drafting.. Elmahdi Mohamed Ali(EMA) research design, critical reading.

Abdelrahim Osman Mohamed (AOM) research design, result interpretation, manuscript drafting and critical reading. All authors read and approved the final manuscript for submission and publication.

Ethics declarations

Ethics approval and consent to participate

Patients enrolled after a written consent was obtained which was approved by the ethical committee of the board of medical and health sciences, University of Khartoum and the ethical committee of the state of Khartoum ministry of health.

Consent for publication

Not applicable.

Competing interests

We have no competing interests.

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