Original Article

Adiponectin and TNFα in relation to glucometabolic control in patients with type 2 diabetes mellitus

Syed Shahid Habib[1], Thamir Al-khlaiwi[1], Huthayfah Al-khliwi[1], Syed Mohammad Habib[2], Syed Abubakar Habib[2], Syed Hamid Habib[3], Adeena Khan[4]

[1]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [2]College of Medicine, Sulaiman Al Rajhi University, Al Bukayriah, Saudi Arabia, [3]Department of Basic Sciences, Khyber Medical University, Peshawar, Pakistan, [4]Department of Radiology, King Saud University, Riyadh, Saudi Arabia

Abstract

Background: The correlation of adiponectin and serum tumor necrosis factor alpha (TNFα) with glucometabolic parameters in diabetes mellitus (DM) needs further studies. We aimed in this study to evaluate the relationship between adiponectin and TNFα with glucometabolic parameters in patients with type 2 DM (T2DM). **Methods:** We conducted a cross-sectional study in the Department of Physiology, College of Medicine, King Saud University, Saudi Arabia. The sample size was 117 from the diabetes clinic of King Abdul-Aziz University hospital through the convenience sampling technique. Subjects were grouped into control (healthy) subjects (53) with no chronic diseases and the diabetic group (64) with confirmed T2DM. Socio-demographic data were collected along with the serum blood sample to analyze the variables. **Results:** Adiponectin was significantly high in healthy subjects compared to the diabetic group (control: 14.4 ± 4.3, T2DM: 11.0 ± 4.1, $P = 0.000$), while TNFα was higher in the T2DM group (7.8 ± 2.7) than in the control group (6.6 ± 2.9, $P = 0.024$). TNFα was negatively correlated with adiponectin in the control group (-0.279) and in diabetic subjects (-0.311) and positively correlated with HbA1c in the diabetic group (0.319) and triglycerides (0.252). Adiponectin was positively correlated with HDL in the control group (0.252) and in diabetic subjects (0.326). There was an inverse correlation between TNFα and adiponectin. **Conclusion:** Adiponectin is higher in healthy subjects than in diabetic patients, while TNFα is higher in diabetic patients. In addition, adiponectin is positively correlated with HDL in healthy as well as diabetic patients. TNFα is positively correlated with HbA1c and triglycerides.

Keywords: Adiponectin, cytokines, diabetes mellitus, glucometabolic control, glycosylated hemoglobin, tumor necrosis factor alpha

Introduction

Diabetes mellitus (DM), as one of the metabolic disorders, is described by elevated glucose plasma levels due to the malfunction of beta cells of the pancreas or to the resistance of insulin in the target cells, or it could be due to both reasons.[1,2]

DM is affected by several risk factors including lifestyle, genetics, and an increased body mass index or obesity [85% of type 2 DM (T2DM) are obese or overweight].[3] One of the main consequences of DM is multiple tissue inflammation. For example, DM can lead to inflammation of the endothelial tissue's inflammation and subsequently the increase of free-radical species.[4-6] In addition, excessive adipose tissue, due to obesity

Address for correspondence: Prof. Syed Shahid Habib, Department of Physiology (29), College of Medicine, PO Box 2925, King Saud University, Riyadh 11461, Kingdom of Saudi Arabia.
E-mail: sshahid@ksu.edu.sa

Received: 30-11-2023 **Revised:** 13-02-2024
Accepted: 23-02-2024 **Published:** 28-06-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1896_23

How to cite this article: Habib SS, Al-khlaiwi T, Al-khliwi H, Habib SM, Habib SA, Habib SH, *et al*. Adiponectin and TNFα in relation to glucometabolic control in patients with type 2 diabetes mellitus. J Family Med Prim Care 2024;13:2741-5.

which is always accompanied DM, can lead to inflammation of adipose tissues and eventually the production of cytokines.[3,6]

The old trend that adipose tissue is only a source of energy has been completely changed with the new discoveries that adipose tissue is an endocrine organ that produces several adipokines that have roles in glucose and lipid metabolism and homeostasis. Some of them have protective roles, especially in metabolic disorders such as adiponectin, while others have detrimental ones such as leptin, resistin, and others.[7,8] The increase of adipose tissue, especially visceral fat, might lead to irregularity of glucose homeostasis and eventually might lead to insulin resistance.[9-11] Adiponectin, an adipokine, is produced by adipose tissue, has several protective roles in various tissues against inflammation, increases insulin sensitivity, and regulates the lipid plasma level. Several researchers have noticed a decreased adiponectin level in obese patients and cardiovascular patients.[12,13] On the other hand, some researchers found a higher level of harmful adiponectin such as tumor necrosis factor α (TNFα) in obese patients.[14] Also, they have noticed that TNFα is not limited to adipose tissue but have an inflammatory role in various body tissues and can interfere with insulin pathways and hence produce insulin resistance.[15-17] More understanding and revealing of the pathways of DM pathophysiology would be of great value to practitioners as well as patients in order to design the appropriate treatment.

We aimed in this study to evaluate the relationship between adiponectin and TNFα with glucometabolic control in patients with T2DM.

Methods

We conducted a cross-sectional study in the Department of Physiology, College of Medicine, King Saud University, Saudi Arabia. The project was approved from the Institutional Review Board (IRB) of the College of Medicine, King Saud University, and informed consent forms were signed by all the subjects. The total sample size was 117 from the diabetic clinic of King Abdul-Aziz University hospital through the convenience sampling technique. We had two groups: control (healthy) subjects (n = 53) with no chronic diseases and the diabetic group (n = 64) with confirmed T2DM. Socio-demographic data were collected from all subjects.

We collected serum blood samples to analyze glycosylated hemoglobin (HbA1c), insulin, triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). In addition, we used a standard sandwich enzyme-linked immunosorbent assay (ELISA) technique using specific monoclonal antibody kits from R and D Systems (Abingdon, United Kingdom) for adiponectin and TNFα. The insulin resistance index of the homeostasis model assessment of insulin resistance (HOMA-IR) was determined using the formula HOMA-IR = (Basal insulin (mU/L) × FBG (mmol/L))/22.5). Body composition analysis was performed in all subjects in the early morning fasting state using bioelectrical impendence analysis with an InBody3.0 (BioSpace, Korea) body analyzer according to the manufacturer's instructions.

Data analysis

Data were analyzed using SPSS version 25, used to analyze data. For continuous variables, means ± standard deviations (SDs) were calculated. We used Student's *t* test to evaluate significant differences between two groups, and for more than two groups, analysis of variance (ANOVA) was used. *Post Hoc* Bonferroni test was used for sub-group comparisons. Correlation was determined by Spearman's correlation analysis for serum TNFα and adiponectin with other variables. A *P* value of <0.05 was considered significant.

Results

The baseline clinical characteristics of the subjects is shown in Table 1. The percent of body fat (% FAT) was significantly lower in the control group (34.9 ± 8.3) compared to the T2DM group (38.0 ± 7.2) with *P* value = 0.038. The body mass index (BMI) was also significantly different between the two groups (control: 28.7 ± 4.4, T2DM: 38.0 ± 7.2, *P* = 0.002). In addition, fat mass is significantly different between the two groups (control: 26.4 ± 8.4, T2DM: 30.0 ± 10.5, *P* = 0.044) and lean body mass (control: 49.3 ± 9.8, T2DM: 48.7 ± 7.8, *P* = 0.713).

Table 2 reveals the biochemical profile of the subjects. Insulin was significantly different between the two groups (control:

Table 1: Demographic and clinical characteristics of all subjects, controls, and patients with T2DM

Variables	All subjects *n*=117	Control, *n*=53	T2DM, *n*=64	*P*
Age (year)	49.4±9.8	48.6±9.5	50.0±10.1	0.437
Height (cm)	160.6±8.6	163.0±8.6	158.7±8.1	0.006
Weight (Kg)	78.0±14.1	76.2±12.8	79.4±15.1	0.220
BMI (Kg/cm2)	30.3±5.3	28.7±4.4	31.6±5.6	0.002
%Body Fat	36.6±7.9	34.9±8.3	38.0±7.2	0.038
Intracellular Fluid (L)	24.3±4.4	24.6±5.0	24.1±3.9	0.561
Extracellular Fluid (L)	11.8±2.5	11.9±3.1	11.8±2.0	0.822
Total Body Water (L)	36.1±6.5	36.3±7.3	35.9±5.8	0.757
Measure Protein Mass (kg)	9.8±1.8	9.9±2.0	9.7±1.6	0.461
Soft lean Mass (Kg)	45.8±8.3	46.1±9.3	45.6±7.4	0.712
Measure Mineral Mass/kg	3.3±0.8	3.4±1.1	3.2±0.4	0.277
Lean Body Mass (Kg)	49.0±8.7	49.3±9.8	48.7±7.8	0.713
Fat Mass (kg)	28.4±9.7	26.4±8.4	30.0±10.5	0.044
Fat Muscle Ratio	0.6±0.2	0.6±0.2	0.6±0.2	0.033
Right Arm	2.1±0.5	2.0±0.5	2.1±0.4	0.600
Left Arm	2.1±0.5	2.0±0.5	2.1±0.4	0.542
Trunk	17.3±3.0	17.2±3.3	17.3±2.8	0.929
Right Leg	5.4±1.1	5.6±1.2	5.3±1.0	0.147
Left Leg	5.4±1.1	5.6±1.2	5.3±1.1	0.158
Physical Fitness score	66.2±6.7	66.6±6.7	65.8±6.7	0.521

Data are represented as mean and standard deviation

6.5 ± 3.3, T2DM: 9.2 ± 10.0, P = 0.047). Adiponectin was significantly different higher in the control (14.4 ± 4.3) compared to T2DM (11.0 ± 4.1, P = 0.000), while TNFα was lower in the control group (6.6 ± 2.9) compared to the T2DM group (7.8 ± 2.7, P = 0.024).

Tables 3 and 4 show the correlation of TNFα and adiponectin with TC, HDL, LDL, TG, glucose, HbA1c, insulin, and proinsulin. TNFα was negatively correlated with adiponectin in the control group (-0.279) and in diabetic subjects (-0.311) and positively correlated with HbA1c in the diabetic group (0.319) and TG (0.252). Adiponectin was positively correlated with HDL in the control group (0.252) and in diabetic subjects (0.326).

Figures 1 and 2 express the box plot for TNFα and adiponectin levels in all subjects, controls, and patients with T2DM grouped into good and poor glycemic control. The effect of glycemic control was non-significant on adiponectin (10.9 ± 4.1 vs 11.2 ± 4.1, P > 0.05) and TNFα (7.6 ± 2.7 vs 8.0 ± 2.7, P > 0.05). Figure 3 shows linear regression relationships of serum adiponectin levels with TNFα in all subjects (a), control subjects (b), and patients with T2DM (c) after controlling for sex and age. An inverse correlation between TNFα and adiponectin was observed.

Table 2: Biochemical profile of all subjects, controls, and patients with T2DM

Variables	All subjects *n*=117	Control *n*=53	T2DM *n*=64	*P*
TC (mmol/L)	5.0±0.8	5.1±0.8	5.0±0.9	0.535
HDL (mmol/L)	1.0±0.3	1.2±0.3	0.9±0.2	<0.001
TG (mmol/L)	1.7±0.8	1.3±0.7	1.9±0.8	<0.001
LDL (mmol/L)	3.2±0.8	3.3±0.7	3.2±0.8	0.476
HbA1c(%)	6.3±1.8	5.0±0.5	7.3±1.8	<0.001
Insulin (microliter/ml)	8.0±7.8	6.5±3.3	9.2±10.0	0.047
Proinsulin µIU/ml	31.3±88.8	11.4±7.9	47.7±117.7	0.017
Adiponectin µg/ml	12.6±4.5	14.4±4.3	11.0±4.1	<0.001
TNFα µIU/ml	7.2±2.8	6.6±2.9	7.8±2.7	0.024
HomaB (%)	70.3±53.4	95.5±61.3	49.4±34.2	<0.001
HOMA-IR	2.5±3.1	1.5±0.8	3.4±3.9	<0.001
FIRI	2.3±2.8	1.3±0.7	3.1±3.5	<0.001

TC=total cholesterol, TG=triglycerides, LDL low-density lipoprotein, HDL=high-density lipoprotein, HOMA-IR=Homeostatic Model Assessment for Insulin, HbA1c=Glycosylated Hemoglobin, TNFα=Serum Tumor Necrosis Factor Alpha

Discussion

Inflammatory responses in T2DM have been linked to poor glycemic and metabolic control. It has been reported in the literature that there is a strong relation between metabolic disorders, especially DM, and tissue inflammation through endothelial cell injury, oxidative stress, and macrophage dysfunction. At the same time, tissue inflammation and its consequences have been suggested to lead to insulin resistance and hence metabolic disorders.[18-24]

Recently, we observed a decrease in inflammatory biomarkers such as inducible nitric oxide synthase (iNOS) and high-sensitivity C-reactive protein (hsCRP), in exercising diabetic patients.[4,5] In addition, we observed that several predictors can be associated with complications of DM patients such as such as adiponectin, resistin, arm circumference, arm muscle circumference, adiponectin–resistin ratio, and insulin resistance adiponectin–resistin ratio.[25-27]

Our study reveals that adiponectin is lower in diabetic patients and is positively correlated with HDL, while TNFα is higher in diabetic patients and positively correlated with HbA1c and TG. Our results are concomitant with the findings of Nayak *et al.*,[28] who observed a decrease in adiponectin with insulin resistance and positive correlation with HDL. In addition, our results come with agreement of Derosa *et al.*,[29] who found correlation of TNFα and metabolic disorders.

As is well known, if adiponectin is a protective adipokine, therapeutic modalities and treatment to increase the level of

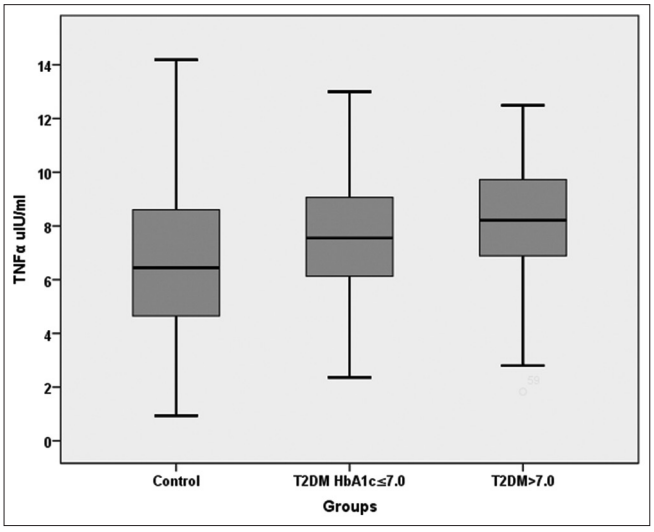

Figure 1: TNFα in all controls and patients with T2DM grouped into good and poor glycemic control

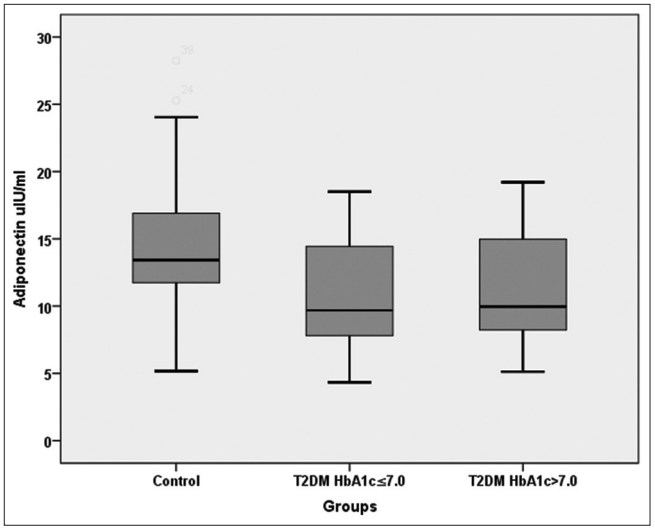

Figure 2: Adiponectin in all controls and patients with T2DM grouped into good and poor glycemic control

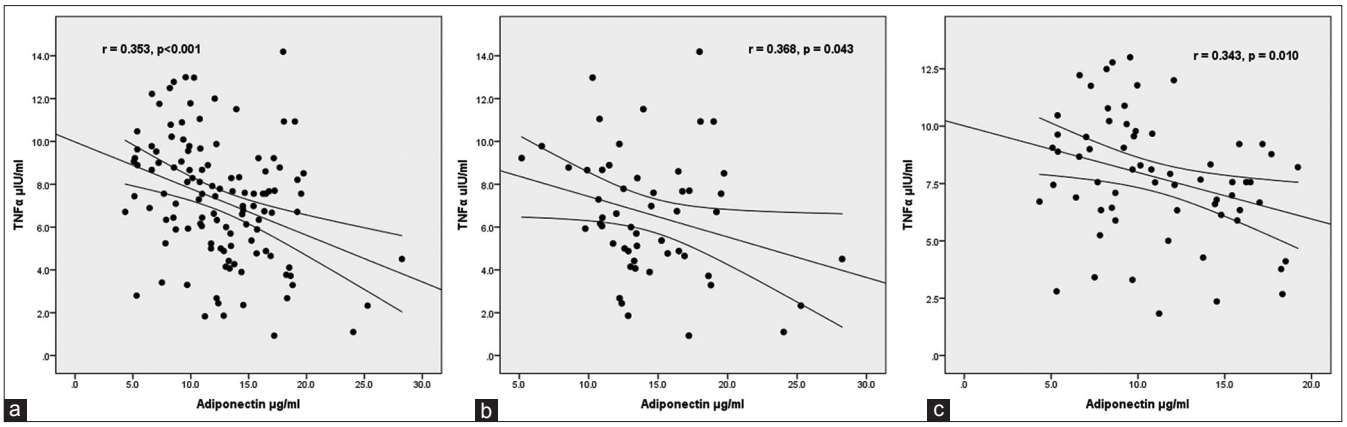

Figure 3: Linear regression relationship of serum adiponectin levels with TNFα in all subjects (a), control subjects (b), and patients with T2DM (c) after controlling for sex and age

Table 3: Spearman's correlation of TNFα with other variables in all subjects, controls, and patients with T2DM

Variables	All subjects	Control	T2DM
Adiponectin	-0.349**	-0.279*	-0.311*
TC	-0.048	-0.076	-0.005
HDL	-0.208*	-0.104	-0.165
TG	0.274**	0.174	0.252*
Glucose	0.264**	0.187	0.223
LDL	-0.107	-0.110	-0.083
HbA1c	0.321**	0.187	0.319*
Insulin	0.170	0.066	0.185
Proinsulin	0.235*	0.097	0.278*

*Correlation is significant at the 0.05 level

Table 4: Spearman's correlation of adiponectin with other variables in all subjects, controls, and patients with T2DM

Variables	All subjects	Control	T2DM
TNFα	-0.349*	-0.279*	-0.311*
TC	0.025	-0.128	0.150
HDL	0.411*	0.252*	0.326*
TG	-0.399*	-0.246	-0.237
Glucose	-0.384*	-0.225	-0.135
LDL	0.086	-0.102	0.198
HbA1c	-0.397*	-0.225	-0.103
Insulin	-0.200*	-0.106	-0.131
Proinsulin	-0.250*	-0.012	-0.100

*Correlation is significant at the 0.05 level

adiponectin should be encouraged, especially in DM patients. In addition, treatment modalities to decrease TNFα in diabetic patients can be introduced in order to control inflammatory consequences of DM.

Even though our study is a cross-sectional study, it is well controlled with a good sample size. In addition, we tried to assess most of the glucometabolic parameters to evaluate the association of adiponectin and TNFα with these variables. Matching of patients for BMI and body composition was one of the limitations of this study as well as restriction of COVID-19 regulations which were great obstacles to expand the study. Large-scale studies with more extended profiles of cytokines involved in the pathways of pathophysiology would be of great interest to be conducted.

Conclusions

Patients with T2DM have lower adiponectin and higher TNFα levels compared to healthy subjects. In addition, adiponectin is positively correlated with HDL in healthy as well as diabetic patients. TNFα is positively correlated with HbA1c and triglycerides.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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