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Impact of Vascular Cell Adhesion Protein-1 (VCAP-1) Levels in Iraqi patients with Type 2 Diabetic Patients

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ABSTRACT— Diabetes mellitus (DM) is a worldwide metabolic disease. Type 2 DM is usually associated with several complications like coronary artery disease, hypertension and dyslipidemia. Atherosclerosis which is considered as a part of macrovascular complications of diabetic patients, is thought to be happened as a result of vascular infiltration of monocytes and lymphocytes with adhesion molecules. These adhesion molecules including VCAM-1 and ICAM-1 which act as atherosclerosis markers and can be isolated from the endothelium and measured in peripheral blood. In addition, it was found that insulin resistance may play a role in endothelial dysfunction where insulin stimulates the release of the adhesion molecules (VCAM-1 and ICAM-1). The aim of this study was to investigate the effect of diabetes mellitus and the safety of anti-hyperglycemic medications on the cardiovascular function in diabetic patients and compare it with the healthy individuals by measuring VCAM-1. About 58 male and female diabetic patients were enrolled in this study (30 patients were already receiving anti-diabetic medications and the 28 patients were just newly diagnosed as DM patients and not yet received treatments), in addition to 30 individuals as healthy control group. The patients' samples were collected from the National Diabetic Center/Al-Mustansiriyah University at the period between March/2017 and May/2017. The mean age for all groups was nearly the same, it was about (52.02 ± 0.81) and the mean BMI for all groups was about (28.77 ± 0.34). Vascular cell adhesion molecule-1 (VCAM-1), insulin, fasting blood glucose (FBG) and HbA1c were all measured for all the three groups. Insulin and VCAM-1 were measured using ELISA technique. In the present study, it was found that there was a high significant difference in the mean VCAM-1 seen in the control group (22.27 ± 0.94) compared with that seen in the newly diagnosed DM patients (18.95 ± 0.58) where (P=0.01), with no significant difference when compared with the mean of already DM patients group receiving treatments (21.08 ± 0.72) besides no significant statistical relationship between means of VCAM-1 of the two DM groups. VCAM-1 showed a negative significant correlation with insulin (P=0.05). From this study, it was observed that VCAM-1 was within normal level when compared with that of healthy control or even below the normal which means that DM is not necessarily associated with increased risk of endothelial dysfunction and atherosclerosis and this dysfunction might be related with some other factors like genes, environmental conditions or other underlying disease states.

KEYWORDS: Adhesion Protein-1, Type 2 Diabetic, Vascular Cell

1. INTRODUCTION

Diabetes mellitus (DM) is a worldwide long – term metabolic disease. Type 2 DM is usually associated with several complications like coronary artery disease, hypertension and dyslipidemia [1]. The incidence of coronary artery disease was found to be higher among diabetic patients in about two to four times compared that in non-diabetics and this will lead to higher mortality rates in diabetic patients [2- 4].

There are many mechanisms that may lead to the progression of myocardial function deterioration in patients with DM such as oxidative stress and hyperglycemia-mediated coronary microvascular dysfunction [5].

The main cause of death among diabetic patients is the cardiovascular disease (CVD) [6]. In diabetic patients, cardiovascular disease is thought to be caused by diabetic microvascular complicatios such as diabetic nephropathy and retinopathy [7- 9].

Cardiac microvascular dysfunction (CMD) can be defined as diminished ability of the heart to pump blood and thus insufficient oxygen requirements. It was found that the incidence of CMD was higher in patients with type 1 or 2 diabetes than non-diabetic patients [10]. Besides the ability of diabetes to cause cardiovascular complications, there were some studies that were done to evaluate the cardiovascular safety of some antihyperglycemic agents and it was found that rosiglitazone is associated with increased risk heart failure and myocardial infarction [11].

Type 1 DM is associated with complete absence of insulin due to autoimmune destruction of islet beta cells of pancreas [12]. Atherosclerosis which is considered as a part of macrovascular complications of diabetic patients, is thought to be happened as a result of vascular infiltration of monocytes and lymphocytes with adhesion molecules. These adhesion molecules including VCAM-1 and ICAM-1 which act as atherosclerosis markers and can be isolated from the endothelium and measured in peripheral blood [13], [14].

In diabetic patients with type 2 DM with uncontrolled diabetes, hyperglycemia can lead to inflammation of endothelium and oxidative stress which in turn may cause microvascular complications such as diabetic retinopathy, diabetic nephropathy, and diabetic kidney disease [15]. This inflammation is thought to be initiated by tumor necrosis factor-α (TNF-α) which in turn stimulate the release of adhesion molecules (VCAM-1 and ICAM-1) [14], [16].

In addition, it was found that insulin resistance may play a role in endothelial dysfunction where insulin stimulates the release of the adhesion molecules (VCAM-1 and ICAM-1) [17]. Under normal conditions, there is a balance between anti- and pro-inflammatory cytokines so those adhesion molecules don't adhere to the endothelial wall, while in diabetic patients, excess glucose will bind with proteins via lysine chain and with oxidative stress this may stimulate the release of adhesion molecules in higher amounts than usual and there adherence to the endothelial wall via their receptors [18].

Type 2 DM patients may prone to obesity as a result of increase in the mass of adipose tissue which is caused by increased size and number of adipocytes. Since adepokine (which is released by adipose tissue) is responsible for regulation of many inflammatory and metabolic processes in the body, in obesity its deregulation may lead to atherosclerosis, DM, and insulin resistance [17].

2. Patients and methods

About 58 male and female diabetic patients were enrolled in this study (30 patients were already receiving anti-diabetic medications and the 28 patients were just newly diagnosed as DM patients and not yet received treatments), in addition to 30 individuals as healthy control group. The patients' samples were collected from the National Diabetic Center/Al-Mustansiriyah University at the period between March/2017 and May/2017.

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The mean age for all groups was nearly the same, for the patients, it was (52.02 ± 0.81) , for the newly diagnosed ones was (52.68 ± 0.81) and for the control group was (52.47 ± 0.78) . BMI (body mass index) was also measured for all groups with the mean BMI for all were also nearly the same, for the patients it was (28.77 ± 0.34), for the newly diagnosed ones was (28.78 ± 0.33) and for the control group was (28.53 ± 0.31). Vascular cell adhesion molecule-1 (VCAM-1), insulin, fasting blood glucose (FBG) and HbA1c were all measured for all the three groups.

Insulin and VCAM-1 were measured using ELISA technique and their kits were Demed tech/Germany for insulin and Rai Biotech Co/US for VCAM-1.

3. Statistical analysis

The Statistical Analysis System- SAS (2012) program was used to detect the effect of different factors on the study parameters. Least significant difference –LSD test (ANOVA) was used to significantly compare between means. Besides, Estimation of correlation coefficient between variables in this study was also determined. The results were expressed in terms of (mean± SE) and P value was also detected, in that $P<0.01$ meant there was a high significant difference and $P<0.05$ meant there was a significant difference [19].

4. Results

In the present study, it was found that there was a high significant difference in the mean VCAM-1 seen in the control group (22.27 ± 0.94) compared with that seen in the newly diagnosed DM patients (18.95 ± 0.58) where (P=0.01), with no significant difference when compared with the mean of already DM patients group receiving treatments (21.08 ± 0.72) besides no significant statistical relationship between means of VCAM-1 of the two DM groups as elucidated in table 1.

In case of insulin, a high significant statistical difference was detected in the two DM groups (26.93 ± 1.04) and (28.51 ± 0.91) compared with the mean insulin level of healthy control group (13.67 ± 0.79) where (P=0.0001) as shown in table 1.

There was a high significant difference in the mean HbA1c in the DM group receiving treatments (10.36 ± 0.34) compared with that of newly diagnosed DM group (8.41 ± 0.09) and that of control (5.16 ± 0.11), and the mean HbA1c in the newly diagnosed DM group was in turn highly significant higher than that of healthy control (P=0.0001) as shown in table 1.

Table 2 showed no significant correlation between age, BMI and the measured VCAM-1, insulin, HbA1c and FBG.

According to the results in table 3. VCAM-1 showed no significant correlation with HbA1c and FBG while it had a negative significant correlation with insulin (P=0.05). On the other hand, insulin showed a high significant positive correlation with HbA1c and FBG (P=0.0001). in addition, HbA1c had a high significant positive correlation with FBG (P=0.0001).

Besides, when age (P=0.848) and BMI (P= 0.823) of the three groups were compared together, it was found no significant difference among the three groups as shown in table 4.

Table 1. Comparison among different groups in study parameters

The Group	No.	Mean ± SE

		VCAM-1 ( )	Insulin ( )	HbA1c ( )	FBG ( )
DM Patients	30	21.08 ± 0.72 AB	26.93 ± 1.04 A	10.36 ± 0.34 A	141.27 ± 2.99 A
Newly Diagnosed DM patients	28	18.95 ± 0.58 B	28.51 ± 0.91 A	8.41 ± 0.09 B	136.14 ± 2.41 A
Control	30	22.27 ± 0.94 A	13.67 ± 0.79 B	5.16 ± 0.11 C	87.47 ± 1.32 B
LSD value	---	2.178 **	2.593 **	0.607 **	6.590 **
P-value	---	0.010	0.0001	0.0001	0.0001
** (P<0.01): high significant., A,B: Duncan letters, A is given to the highest significant value. LSD: Least significant difference					

Table 2. Correlation coefficient between age, BMI and other Parameters:

Parameters	Age (year)		BMI (m/kg^2)	
	Correlation coefficient-r	P-value	Correlation coefficient-r	P-value
VCAM-1	-0.05	0.642 NS	0.08	0.467 NS
Insulin	0.04	0.678 NS	0.06	0.548 NS
HbA1c	-0.02	0.876 NS	0.09	0.386 NS
FBG	-0.06	0.557 NS	0.12	0.258 NS
NS: Non-Significant.				

Table 3. Correlation coefficient among study parameters:

Parameters	Correlation coefficient-r	P-value
VCAM-1 & Insulin	-0.21	0.050 *
VCAM-1 & HbA1c	-0.14	0.187 NS
VCAM-1 & FBG	-0.17	0.104 NS
Insulin & HbA1c	0.76	0.0001 **
Insulin & FBG	0.72	0.0001 **
HbA1c & FBG	0.78	0.0001 **
* (P<0.05), ** (P<0.01), NS: Non-Significant.		

Table 4. Comparison between age and BMI among the groups:

Variable	The Group	No.	Mean ± SE	Range
Age (year)	Patient	30	52.02 ± 0.81	44.00-59.00
	Newly Diagnosis	28	52.68 ± 0.81	44.00-60.00
	Control	30	52.47 ± 0.78	44.00-60.00
	LSD value	---	2.275 NS	---
	P-value	---	0.848	---
BMI (m/kg^2)	Patient	30	28.77 ± 0.34	25.40-32.90
	Newly Diagnosis	28	28.78 ± 0.33	25.40-32.90

	Control	30	28.53 ± 0.31	25.40-32.90
	LSD value	---	0.929 NS	---
	P-value	---	0.823	---
NS: Non-Significant.				

5. Discussion

This study was applied on diabetic patients who were already had DM and receiving anti-diabetic treatments and other patients who were just newly diagnosed as DM and net yet received treatments to detect the level of VCAM-1, insulin, HbA1c, and FBG in those patients and compare it with that of healthy subjects who were designed as control, beside the effect of BMI and age on those parameters.

From the results, the current study found that VCAM-1 in the two DM patients' groups was less than that of healthy control and this is not agreed with other studies which detected that VCAM-1 as adhesion molecule is increased in DM patients that leads to endothelial dysfunction as a part of inflammatory process [13], [14].

The insulin resistance level is needed to investigate for hyperglycemis even before DM diagnosis [20].

This study also found that insulin in DM patients' groups was higher than in control group and this might be due to increased insulin resistance in those patients.

HbA1c in turn was higher in DM patients with treatments compared with its level in newly diagnosed ones and healthy subjects and this agreed with other study which stated that glycated Hb (HbA1c) don’t reach level below 7% in most DM patients [21].

In the present study, it was found that body mass index (BMI) and the age of the patients had no significant correlation with the measured parameters. This might not in agreement with another study which detected that as BMI and fat mass of the patients and their ages increased, the risk of developing DM complications was increased [22].

According to the current study, VCAM-1 showed negative correlation with insulin which means that as insulin level increased, VCAM-1 levels decreased and vice versa and this might not agree with other study which demonstrated that insulin resistance would increase the expression of adhesion molecules like VCAM-1 [23]. Whereas insulin showed a high positive correlation with HbA1c and FBG and this result was expected since DM patients usually have elevated HbA1c, FBG and increased insulin as a result of insulin resistance.

6. Conclusion

From this study, it was observed that VCAM-1 was within normal level when compared with that of healthy control or even below the normal which means that DM is not necessarily associated with increased risk of endothelial dysfunction and atherosclerosis and this dysfunction might be related with some other factors like genes, environmental conditions or other underlying disease states.

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