

Circulating Cell Adhesion Molecules Level in Type 2 Diabetes Mellitus and Its Correlation with Glycemic Control and Metabolic Syndrome: A Case-control Study

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Abstract

Background: Early detection of high levels of endothelial biomarkers may help in the design of new strategies to prevent many disease complications, as these biomarkers could enable early prediction of endothelial dysfunction and activation. **Objectives:** This study aimed to detect the level of circulating cell adhesion molecules (ICAM-1, VCAM-1) in diabetic patients and to investigate its relation to glycemic control, duration of diabetes mellitus, and metabolic syndrome. **Materials and Methods:** Age and sex-matched case-control study design was adopted, the case group involved (type 2 diabetes mellitus on oral hypoglycemic agent only and free from other medical problems), and the control group was (the healthy people without a family history of diabetes mellitus). The samples were collected between November 2021 and May 2022. Both ICAM-1 and VCAM-1 were measured in both groups. **Results:** A total of 160 individuals were involved (80 cases and 80 controls). The level of both ICAM-1/VCAM-1 was higher in patients with type 2 diabetes mellitus with a value of $P < 0.0001$. There was a strong association between ICAM-1, VCAM-1, and HbA1c. As the duration of the disease increases, the level of these molecules increases. The level of VCAM-1 in patients with metabolic syndrome was very high, whereas for ICAM-1 a slight increase was observed. **Conclusion:** Circulating cell adhesion molecules can be considered as a marker for detecting the risk of occurrence of diabetes mellitus and the level of these markers can be helpful in follow-up of cases with diabetes and giving a guide for risk of occurrences of metabolic syndrome.

Keywords: Atherosclerosis, cell adhesion molecules, diabetes mellitus, metabolic syndrome

INTRODUCTION

Cell adhesion molecules (CAMs) have been found in a wide range of cell types, including endothelium, lymphocytes, macrophages, and several tumor cell lines.^[1] As such molecules can be expressed nonspecifically throughout the circulatory system, the plasma concentration of circulating CAMs revealed total body atherosclerotic load. Cellular adhesion, which allows cells to clump together to create tissues, can also help the immune system distinguish between self and non-self-cells. Abnormal cellular adhesion could be a sign of health issues.^[2]

Soluble adhesion molecules levels in the blood are linked to hyperglycemia, insulin resistance, dyslipidemia, and obesity, as well as the development of nephropathy, retinopathy, myocardial infarction, and stroke, and the obliteration of peripheral artery disease in type 1 and 2

diabetes.^[3] Given their significance in the genesis of tissue damage and endothelial dysfunction associated with diabetes, these molecules could be used as a target of therapeutics to prevent the genesis and advancement of diabetic problems.^[3]

After controlling all other risk factors, a recent meta-analysis and systematic review discovered that with type 2 diabetes E-selectin and plasma soluble ICAM-1 were independently related. The majority of prospective

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diabetes studies have been limited to just a small number of CAMs and have primarily been undertaken. The relationships between six CAMs (ICAM-1, VCAM-1, E-selectin, L-selectin, P-selectin, and E-cadherin) and the risk of diabetes, as well as whether ethnicity/race influenced any of them, were studied.^[4]

Endothelial dysfunction is associated with diabetes, and the presence of higher CAMs in diabetic individuals without micro- or macrovascular problems shows an activated endothelium, which is linked to the release of endothelial products, which can be linked to the development of microangiopathy.^[1] Many epidemiological studies have found a positive and independent link between the onset of type 2 diabetes and levels of soluble CAM.^[5,6]

In diabetic patients, strict glycemic control decreases the risk of microvascular disease, and long-term treatment and follow-up research have shown that strict glycemic control is associated with a lower risk of cardiovascular diseases.^[7,8] Many factors influence blood glucose levels, and therefore, the reasons for poor glycemic control are diverse and complex.^[9]

Studies directed at the detection of the mechanism of diabetic complications could lead to a better understanding for better selection of antidiabetic medication and its earlier application to prevent disease progression and complication.^[10]

Thus, this study was designed to detect the plasma concentration of CAM in type 2 diabetes compared with its level in an apparently healthy person and to show if their levels have any correlation with the duration of disease, glycemic control, and presence of the metabolic syndrome.

MATERIALS AND METHODS

Study design

To achieve the aim of this study, a 1:1 age and sex-matched case-control study was conducted in the diabetic unit at Azadi Teaching Hospital, Duhok city, in the Kurdistan region of Iraq. The case group includes those individuals that have been diagnosed as having type 2 diabetes mellitus for more than 6 months, and people who were using oral hypoglycemic agent only as treatment, and not having any other medical problems. Also, the control group involved those individuals who were apparently healthy without a family history of diabetes mellitus and not receiving any drugs. The samples were collected between November 2021 and May 2022.

Of all participants, only 160 individuals met the inclusion criteria of the study (80 cases and 80 controls); 35 out of 80 were women and the other 45 were men for each group. In the case group, the lower limit of age was 33 years for men and 37 years for women; whereas the upper limit of age was 70 years for men and 71 years for women. The lower limit of

age in the control group was 33 years for men and 36 years for women; whereas the upper limit of age was 69 years for men and 70 years for women. All cases and controls underwent the same laboratory tests after they met the study criteria. The level of CAM (ICAM-1/VCAM-1) was measured in both groups. Then, their levels were compared with the duration of disease, good or bad glycemic control, and presence or absence of metabolic syndrome in diabetic patients.

Data collection

Venous blood samples (4cc) were withdrawn from all cases and controls (after an overnight fasting); 1cc for the lavender tube for the HbA1c test, and other 3cc for the red tube for the lipid profile test and circulating cell adhesion laboratory tests. Lipid profile and HbA1c were calculated by Cobas b 101 systems. In addition, fasting blood glucose was performed for all participants using a glucometer. Blood pressure, weight, height, and waist circumference were also measured.

Tests principle (ICAM-1/VCAM-1)

Sandwich-ELISA kits were used; the provided kits contain micro-ELISA plates coated with specific antibodies for humans (ICAM-1/CD54, VCAM-1/106). Then, samples or standards were combined with a specific antibody in the micro-ELISA plate wells. A biotinylated observation of a specific antibody for humans (ICAM-1/CD54, VCAM-1/106) and Avidin-Horseradish Peroxidase (HRP) conjugate was successively added to each microplate well and then incubated for 1 h and washed away of the free components (three times). The solution of the substrate was prepared to be added to each well. Only wells with human (ICAM-1/CD54, VCAM-1/106), biotinylated detection antibodies, and Avidin-HRP conjugate will appear blue in color. Next, stop solution was added to terminate the enzyme-substrate reaction and turn the color to yellow. The measured optical density (OD) with a wavelength of 450 ± 2 nm was proportional to the total concentration of humans (ICAM-1/CD54, VCAM-1/106). Also, the concentration of humans (ICAM-1/CD54, VCAM-1/106) in the samples was calculated by comparing the OD of the samples to the standard curve.

Ethical consideration

This study was approved by the Research Ethics Committee of Duhok Directorate General of Health, Department of Planning and Scientific Research Division on November 10, 2021; reference number 1011. All patients were informed about the aim of the study and the procedure details. Patients who agreed to participate in the study signed the consent form provided by the Research Ethics Committee.

Statistical analyses

The homogeneity for general information between T2DM and healthy controls was examined in an independent

t-test. The correlations of circulating CAMs with glycemic control in patients with type 2 diabetes mellitus were examined in bivariate regression. The comparisons of circulating CAMs in T2DM patients with different disease duration were examined by analysis of variance (ANOVA) one-way. The post hoc comparisons were performed in a Tukey test. The predictors of ICAM-1 and VCAM-1 were examined in standard least squares with affect leverage. The significant level of difference was determined by a value of $P < 0.05$. The statistical calculations were performed in JMP Pro 14.3.0.

RESULTS

A total of 160 persons were involved in this study (after excluding those who did not meet the inclusion and exclusion criteria of the study). The participants were divided into two groups: 80 cases and 80 controls. The mean (SD) age was nearly similar—54.76 (8.84) and 54.4 (8.95) for the case and control groups, respectively. The gender of participants was 45 (56.25%) men and 35 (43.75%) women for each group. Considering smoking status, 18.75% of the case group and 20% of the control group were smokers. For the case group, 11.25% were heavy smokers while for the control group 15% were heavy smokers with no statically significant differences between the two groups. Regarding body mass index, the percentage of normal weight 27.5% and overweight 45% was higher among the control group while the percentage of obese 43.75% was higher among the case group with a $P = 0.035$.

The mean of both ICAM-1 and VCAM-1 was higher among diabetic cases when compared with controls (33.63 vs. 12.49 and 109.34 vs. 29.00, respectively) with a P -value < 0.0001 [Table 1].

In diabetic patients, there was a strong linear association (0.68, $P = 0.00005$) between ICAM-1 and HbA1c with 95% confidence interval (CI) recorded as (0.54, 0.78). Likewise, a strong linear association (0.66, $P = 0.00002$) was observed between VCAM-1 and HbA1c with a 95% CI of (0.50, 0.76) [Table 2]. There was no increase in the level of ICAM-1 in parallel to the increase in the levels of total cholesterol and low-density lipoprotein (LDL). An approximate similar correlation was observed for VCAM-1, while there was an insignificant increase in its level with total cholesterol and LDL levels. There was an extreme correlation between ICAM-1 and TG as the level of ICAM-1 largely increases with an increase of TG and the relation was similar for VCAM-1. An opposite relation was noticed between HDL and circulating CAMs (ICAM-1, VCAM-1); the levels of these molecules decrease as HDL levels increase [Figures 1 and 2].

Considering the duration of the presence of diabetes mellitus and the levels of the circulating cell adhesions molecules, the mean of both ICAM-1 and VCAM-1 increases as the duration of the disease increases with a significant P -value. The mean of the 1–5 years' duration group was lower for ICAM-1 and VCAM-1, whereas the mean of the 10–15 years' duration group was higher for both ICAM-1 and VCAM-1 [Table 3].

Regarding diabetic patients with or without metabolic syndrome, the level of VCAM-1 was higher among patients with metabolic syndrome ($P = 0.019$), 95% CI was recorded as (99, 109), while for ICAM-1 a slight increase in its level was observed [Table 4].

The lowest level of ICAM-1 and VCAM-1 was seen among patients on sitaglipatin with metformin and metformin only while highest level of mentioned molecules was observed

Table 1: Comparisons of circulating CAMs between patients with type 2 diabetes mellitus and healthy control

Characteristics ($n = 160$)	Study groups mean (SD)				P -value (two-sided)
	T2DM ($n = 80$)	95% CI	Control ($n = 80$)	95% CI	
ICAM-1	33.63 (8.32)	31.78–35.48	12.49 (2.49)	11.94–13.04	$< 0.0001^a$
VCAM-1	109.34 (13.20)	106.40–112.28	29.00 (9.37)	26.91–31.08	$< 0.0001^a$

CAM: cell adhesion molecule, SD: standard deviation, CI: confidence interval

^aAn independent *t*-test was performed for statistical analyses

Table 2: Correlations of circulating CAMs with glycemic control in patients with type 2 diabetes mellitus

Independent factors	Outcomes	
	ICAM-1	VCAM-1
HbA1c		
<i>r</i> -value	0.6826	0.6510
P -value	< 0.0001	< 0.0001
95% CI (lower, upper limit)	0.5445, 0.7846	0.5032, 0.7618

CAM: cell adhesion molecule, CI: confidence interval. Bivariate regression was performed for statistical analyses

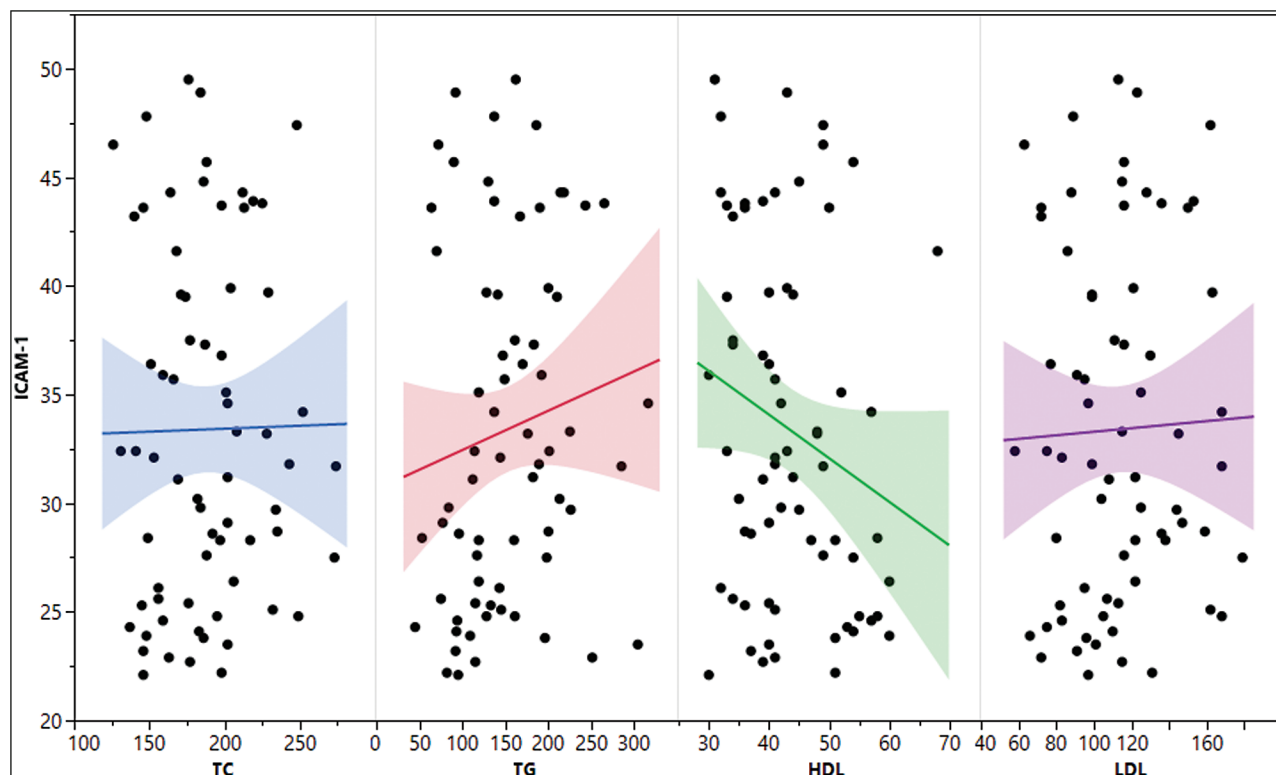


Figure 1: Correlation between ICAM-1 and lipid profiles in diabetic patients

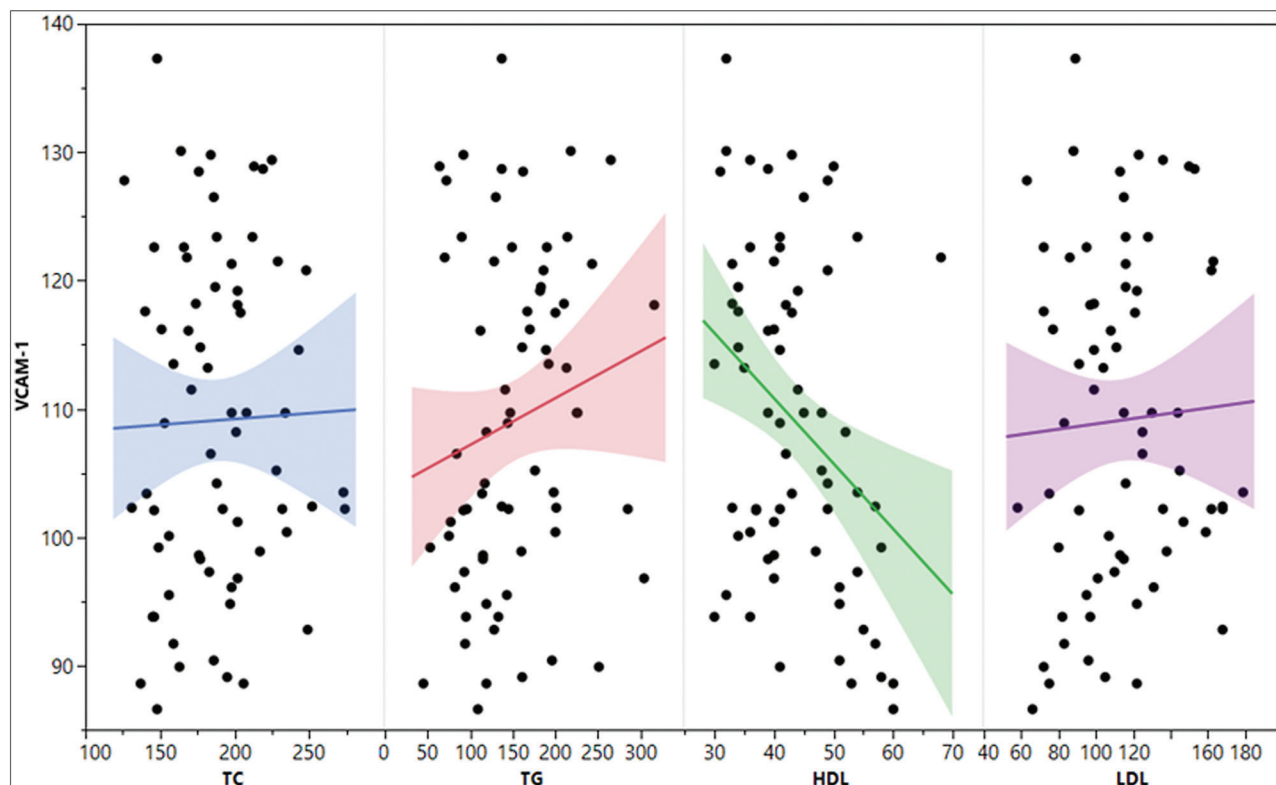


Figure 2: Correlation between VCAM-1 and lipid profiles in diabetic patients

Table 3: Comparisons of circulating CAMs in type 2 diabetes mellitus patients with different disease durations

Duration	ICAM-1			Pairwise comparisons
	Mean	SD	P-Value	
Disease duration			<0.0001	
1–5 years	28.27	5.02		10–15 years vs. 1–5 years (P < 0.0001)
5–10 years	34.81	7.38		15–20 years vs. 1–5 years (P = 0.0026)
10–15 years	45.45	4.15		10–15 years vs. 5–10 years (P < 0.0001)
15–20 years	41.65	3.04		5–10 years vs. 1–5 years (P < 0.0001)
Duration	VCAM-1			Pairwise comparisons
	Mean	SD	P-Value	
Disease duration			<0.0001	
1–5 years	102.35	9.87		10–15 years vs. 1–5 years (P < 0.0001)
5–10 years	111.46	11.88		15–20 years vs. 1–5 years (P = 0.0049)
10–15 years	127.85	4.25		10–15 years vs. 5–10 years (P < 0.0001)
15–20 years	123.80	7.92		5–10 years vs. 1–5 years (P = 0.0006)

CAM: cell adhesion molecule, SD: standard deviation. Analysis of variance (ANOVA) one-way was performed for statistical analyses. The post hoc comparisons were performed in a Tukey test

Table 4: Comparison of CAMs in type 2 diabetes mellitus with and without metabolic syndrome

Characteristics (n = 160)	Metabolic syndrome mean (SD)				P-Value (two-sided)
	Metabolic syndrome (n = 51, 63.8%)	95% CI	Normal (n = 29, 36.2%)	95% CI	
ICAM-1	34.58 (8.13)	32.29–36.87	31.96 (8.53)	28.71–35.20	0.1764
VCAM-1	111.91 (12.56)	108.38–115.45	104.82 (13.30)	99.76–109.88	0.0199

CAM: cell adhesion molecule, SD: standard deviation, CI: confidence interval. An independent *t*-test was performed for statistical analyses

Table 5: Comparisons of circulating CAMs in T2DM with different drug intake

OHA	ICAM-1 mean (SD)				P-Value (two-sided)
	Number	No	Number	Yes	
Metformin only	51	35.27 (8.31)	29	29.39 (5.94)	0.0017
Glimepiride 4mg and metformin	34	31.18 (7.98)	46	35.44 (8.19)	0.0226
Metformin and sitagliptin 100mg only	77	33.84 (8.26)	3	28.33 (10.02)	0.2639
Glimepiride 4mg only	78	30.53 (7.74)	2	35.70 (8.12)	0.0057
OHA	VCAM-1 mean (SD)				P-Value (two-sided)
	Number	No	Number	Yes	
Metformin only	51	112.05 (13.71)	29	102.84 (9.09)	0.0024
Glimepiride 4mg and metformin	34	105.56 (11.80)	46	112.14(13.61)	0.0266
Metformin and sitagliptin 100mg only	77	109.63 (13.18)	3	102.00(14.02)	0.3293
Glimepiride 4mg only	78	104.33 (10.99)	2	112.68(13.59)	0.0049

CAM: cell adhesion molecule, OHA: oral hypoglycaemic agents, SD: standard deviation. An independent *t*-test was performed for statistical analyses

in categories receiving glimepiride and glimepiride with metformin [Table 5].

DISCUSSION

This study revealed that the level of CAM (both ICAM-1 and VCAM-1) was higher for pure diabetic patients when compared with the control group. Similar findings were detected by other case-control studies conducted on a diabetic patient with microangiopathy, which reveals that the serum levels of both sICAM-1 and sVCAM-1 are elevated in diabetes mellitus patients and shows that these

molecules may have a role in the pathogenesis of diabetic microvascular complications.^[11] A study conducted on 58 type 2 diabetic patients with microvascular complications and 20 age-matched healthy subjects showed that isolated endothelial cells from diabetic patients express higher amounts of VCAM-1 and ICAM-1.^[12] This increase in the level of circulating adhesion molecules reflects endothelial damage due to the positive relationship between those molecules and endothelial cells.

In this study, the glycemic control was measured and it reveals that the level of both molecules ICAM-1 and

VCAM-1 was positively and strongly related to HbA1c; poor glycemic control leads to an increase in the level of these molecules, which is because the long duration of uncontrolled hyperglycemia aggravates glycemic control and increases the level of these molecules. Another study conducted in euglycemic hyperinsulinemic clamp in three different groups without additional cardiovascular risk factors showed that the increased E-selectin concentrations are related to hyperglycemia, hyperinsulinemia, and insulin resistance, whereas increased ICAM-1 and VCAM-1 plasma concentrations in patients with type 2 diabetes are rather related to hyperglycemia than to hyperinsulinemia or insulin resistance.^[13] Some studies support the hypothesis of elevating the level of VCAM-1 in diabetic patients with disease complications such as macrovascular and diabetic kidney disease; this is because isolated endothelial cells from diabetic patients express a higher amount of VCAM-1 than ICAM-1.^[12,14] On the contrary, a study found that even after correcting for glycemic control, CAMs, particularly ICAM-1 and P-selectin, may be independent contributors to the development and progression of diabetic neuropathy. A significant adverse relationship was found between E-selectin, P-selectin, PNCV, and ICAM-1.^[15]

A strong correlation was shown in the current study between the presence of dyslipidemia and soluble circulating adhesion molecules (ICAM-1, VCAM-1), particularly for HDL-cholesterol and triglycerides. Increased expression of CAMs on the vascular endothelium was postulated to play an important role in atherogenesis. Both *in vitro* and *in vivo* studies have suggested that dyslipidemia may increase the expression of CAMs.^[16] This study revealed that the high LDL-C level and hypertriglyceridemia were observed among patients with poor glycemic control; a similar finding was detected by a study conducted in Duhok city among diabetes patients.^[17]

In accordance with other studies, our study demonstrates that an increase in the level of soluble ICAM-1 and VCAM-1 was independently correlated with hypertriglyceridemia.^[16,18] For HDL-cholesterol, as the level of these molecules decreases the HDL-cholesterol increases. This study also revealed that a marked increase in the level of soluble CAMs was not observed for total cholesterol and LDL-cholesterol; this may be due to a small number of participants suffering from the elevated level of total cholesterol and LDL-cholesterol. Atherosclerosis is one of the major problems that can affect health; till now it is not clear whether the endothelial dysfunction caused by dyslipidemia results in increased expression of CAMs and increased release of these molecules into the plasma or whether the increased levels of soluble CAMs were a consequence of atherosclerosis induced by dyslipidemia.

Regarding the duration of disease, our study detects that there was a higher level of these molecules observed in the group with a long duration of diabetes mellitus. Many

other studies noticed that there was a low level of these molecules in cases with a shorter duration of disease.^[19,20]

Metabolic syndrome characteristics include the presence of obesity and insulin resistance whereby the body mounts a supranormal insulin response to a glucose load.^[21] The patients with metabolic syndrome in this study expressed a higher level of VCAM-1 and ICAM-1 than those without metabolic syndrome. This finding was consistent with a study carried out for metabolic syndrome patients with cardiovascular diseases.^[22] As expected, the patients with metabolic syndrome showed an increase in the level of triglycerides and a reduced level of HDL-cholesterol level. In this study, those patients with reduced HDL-cholesterol and increased triglycerides showed higher levels of circulating adhesion molecules (ICAM-1, VCAM-1). A recent meta-analysis study showed that elevated levels of these molecules increase the risk of development of type 2 diabetes mellitus in the general population regardless of their role in the development of atherosclerosis in diabetic and cardiovascular patients.^[23,24] This study showed that the level of circulating CAMs was higher in those receiving metformin and glimepiride when compared with those on other oral hypoglycemic drug. Another study showed insignificant difference in the level of ICAM-1 and VCAM-1 in those using sitagliptin and metformin.^[25] A study conducted in 2006 to detect the glimepiride efficacy on insulin resistance, adipocytokines, and atherosclerosis revealed an improvement in levels of ICAM-1 and VCAM-1 and improvement of endothelial functions due to biosynthesis of nitric oxide.^[26] The limitation of this study was the size of the population. It was difficult to collect larger numbers of patients with pure diabetes mellitus without any other diseases and those were considered as controls that were healthy without a family history of diabetes.

CONCLUSIONS

Alterations in the hemostasis and the systemic inflammatory process may increase the risk of cardiovascular events and metabolic syndrome in diabetic patients. Therefore, the identification of early predictive markers may help reduce diabetes-related vascular complications. The cellular adhesion molecules can be used as a marker for early diagnosis of cases of diabetes mellitus; in addition to that they can give a guide for better therapy and prognosis.

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Conflicts of interest

There are no conflicts of interest.

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