Study of Adhesion Molecules in Type 2 Diabetes Mellitus Iraqi Patients with Dyslipidemia

DOI: https://doi.org/10.32007/jfacmedbagdad.6622273

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Abstract:

**Background:** Cell adhesion molecules are protein entities that are located on the cell surface. The vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) expression is related to type 2 diabetes mellitus (T2DM) with dyslipidemia.

**Objectives:** To determine the levels of VCAM-1 and ICAM-1 in T2DM patients with dyslipidemia and to explore the relationship between VCAM-1 and ICAM-1 and the development of dyslipidemia in T2DM patients.

**Patients and methods:** The study included 150 individuals with an age range of (35-55) years. Patients with diabetes for more than 5 years were excluded. Fifty healthy individuals constituted Group 1 (G1), fifty patients with T2DM constituted Group 2 (G2), and fifty T2DM patients with dyslipidemia constituted Group 3 (G3). Whole blood samples were drawn to measure HbA1c based on fluorescence immunoassay technology. The serum was separated to measure fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), and high-density lipoproteins (HDL) by manual methods, while VCAM-1, and ICAM-1 were determined using the ELISA test. The study was conducted between November 2022 and April 2023 at the National Center for Diabetes Treatment and Research, Baghdad, Iraq.

**Results:** Significantly higher levels of FSG and HbA1c were detected in G2 and G3 compared to G1, but non-significantly so when G3 was compared to G2. Significant higher levels of TG and TC levels were detected for G3 when compared to G1 and G2, but non-significantly so when G2 was compared to G1. HDL levels were significantly lower in G3 compared to G2 and G1, but non-significantly so when G2 was compared to G1. VCAM-1, and ICAM-1 were significantly higher in G2 compared to G1, and VCAM-1 level was significantly higher in G3 compared to G2. Non-significant differences in ICAM-1 levels were found between G3 and G2.

**Conclusion:** VCAM-1 and ICAM-1 are potentially significant factors in the development of dyslipidemia in diabetes patients. They might serve as biomarkers to accurately predict the progression of cardiovascular disease.

**Keywords:** Diabetes mellitus; Dyslipidemia; VCAM-1; ICAM-1.

Introduction:

The characteristic of diabetic dyslipidemia is hyperglycemia with lipoprotein abnormalities. Over 70% of those who have T2DM are affected by dyslipidemia making it a fairly common condition. Diabetes confers a greatly increased risk of cardiovascular disease (1,2).

The VCAM-1 is a protein that also contains T-cell receptors and antibodies (3). Studies demonstrate relationships among the sVCAM-1 and sICAM in patients of T2DM with cardiovascular disease (CVD) and revealed that abnormalities in endothelium cause a rise in these markers (4,5). The ICAM-1 is a glycoprotein that is found in microglial cells, astrocytes, central nervous system in addition to endothelial cells (white and grey human forebrain) (6,7).

Because of dyslipidemia, cholesterol builds up and becomes oxidized, which speeds up the activation of ICAM-1 for monocyte adhesion. This causes a rise in the number of monocytes and production of cytokines (8). Hyperglycemia and dyslipidemia that last for an extended time both contribute to oxidative stress rise, which increases the production of oxidized low-density lipoprotein, stimulates immunological cells, and increases the levels of VCAM-1 and ICAM-1, which contribute to the creation of foam cells (9). Many researches demonstrated that VCAM-1 and ICAM-1 are involved in the development of microvascular issues (10,11).

The purpose of this study was to determine the levels of VCAM-1 and ICAM-1 in T2DM with and without dyslipidemia, the findings of which may be helpful in the follow-up care of diabetic patients with dyslipidemia and in preventing the development of CVD.

Patients and Methods:

One hundred and fifty participants were included in the study with an age range of (35-55) years. They were divided into three groups: Group 1 (G1)
consisting of 50 healthy individuals (control group), Group 2 (G2) consisting of 50 T2DM patients with no dyslipidemia, and Group 3 (G3) consisting of 50 T2DM patients with dyslipidemia. Venous blood samples (5 milliliters) were collected from each participant in the three groups from November 2022 to April 2023 at the National Center for Diabetes Treatment and Research, Baghdad, Iraq. The blood samples were used to measure HbA1C by the fluorescence immunnoassay technology and the levels of VCAM-1 and ICAM-1 by the ELISA test (Mybiosource / USA). The concentrations of serum FBG, TG, TC, and HDL were determined by manual procedures.

The Statistical Packages of the Social Sciences, version 21 (SPSS-21) was used for statistical analysis, with P < 0.05 accepted as significant. Quantitative variables were correlated using Pearson's correlation. The t-test was used to test the difference between two independent means. The mean for G3 is higher than G2. The mean levels of ICAM-1 for G2 and G3 were higher than for G1, but they were not significantly different for G2 and G3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>G1 n (50)</th>
<th>G2 n (50)</th>
<th>G3 n (50)</th>
<th>G1&amp;G2</th>
<th>G1&amp;G3</th>
<th>G2&amp;G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL)</td>
<td>89.0±8.82</td>
<td>184.5±8.41</td>
<td>211.5±8.29</td>
<td>S</td>
<td>S</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HbA1c%</td>
<td>4.9±0.43</td>
<td>8.5±1.95</td>
<td>8.8±1.79</td>
<td>S</td>
<td>S</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>93.5±15.77</td>
<td>101.5±33.89</td>
<td>237.9±51.88</td>
<td>NS</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>156.1±26.3</td>
<td>175.3±33.14</td>
<td>216.0±35.54</td>
<td>NS</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>51.5±7.41</td>
<td>46.2±10.90</td>
<td>31.2±4.45</td>
<td>NS</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: The mean levels of VCAM-1 and ICAM-1 in the three study groups

Correlation of VCAM-1 and ICAM-1

Table (3) and figure (1) show a highly significant positive correlation between VCAM-1 and ICAM-1 in G1 (r = 0.531) and G2 (r = 0.381). A negative non-significant correlation was found in G3 (r = -0.131).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>VCAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1</td>
<td>G1</td>
</tr>
<tr>
<td></td>
<td>r = 0.531 (HS)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
</tr>
<tr>
<td></td>
<td>r = 0.381 (S)</td>
</tr>
<tr>
<td></td>
<td>G3</td>
</tr>
<tr>
<td></td>
<td>r = -0.131 (NS)</td>
</tr>
</tbody>
</table>

Results:

The results of the FSG, HbA1c, TG, also HDL tests are shown in table (1). There was a significant difference between the means of FBG and HbA1c in G2 and G3 compared to G1. No such difference was found between G3 and G2. The table also shows that the mean TG level in G3 (237.9 ng/mL) was significantly higher than in G1 (93.5 ng/mL) and G2 (101.5 ng/mL). The means of G2 and G1 were not significantly different. The mean TC levels in G1 (156.1) and G2 (157.3 ng/mL) were significantly higher than in G3 (216.0 ng/mL). However, the difference between G2 and G1 was not significant, compared to G2 and G1, the mean HDL level in G3 was significantly lower. The mean levels of G2 and G1 were not significantly different.

Table 1: Mean levels of FBG, HbA1c, TG, TC, and HDL in the three study groups
Figure (1): Correlations between VCAM-1 and ICAM-1 in the three study groups

Receiver Operating Characteristic (ROC): For VCAM-1: ROC curve analysis of VCAM-1 in the three study groups reveals an impressive area under the curve (AUC) of 0.87, which is significant at 95% with a p-value of 0.0081, which is less than the 0.01 threshold. The VCAM-1 optimal cut-off value is 1926. The sensitivity and specificity were 91% and 86%, respectively, as shown in table (4) and figure (2). The results demonstrate high accuracy levels in discriminating between the three groups, and the efficacy of the VCAM-1 test among three groups.

Table 4: sensitivity and specificity for VCAM-1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under the curve</th>
<th>Accuracy</th>
<th>Cut off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1</td>
<td>0.91</td>
<td>0.86</td>
<td>0.87</td>
<td>0.79</td>
<td>0.95</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>0.90</td>
<td>0.73</td>
<td>0.76</td>
<td>0.65</td>
<td>0.86</td>
</tr>
</tbody>
</table>

1- For ICAM-1: ROC curve analysis shows a value of 0.76 AUC that is significant at 95% with a 0.007 p-value, which is less than the threshold of 0.01. The ICAM-1 optimal cut–off value was 2.23. The sensitivity and specificity were 90% and 73%, respectively. This shows a high accuracy in recognition between the three groups and the test efficacy among the groups, table (4) and figure (3).

Figure (2): ROC for VCAM-1

Figure (3): ROC for ICAM-1
Discussion:
The findings of the current study, reveal that diabetic patients had greater levels of FBG and HbA1c than the control which is supported by a number of other investigations (12–14). This may indicate that those diabetics were not well-controlled. Several studies have indicated that diabetics have greater rates of dyslipidemia, a condition that is related to hyperglycemia, increased HbA1c in blood, and hypercholesterolemia (15). This condition affects the ability of the body to process fats. Diabetics have abnormal lipid profiles and high HbA1c levels (16, 17). The abnormalities of lipids include low HDL and high TG and TC (18, 19). The findings of the current study agree with previous studies which showed that dyslipidemia is more common in T2DM cases (20–22). Dyslipidemia contributes to CVD development due to the persistent buildup of lipid plaques on arterial walls (23,24). The findings on the effect of HDL on the upregulation of VCAM-1 messenger RNA inside human umbilical vascular endothelial cells were recently made public with participants representative of the general population (25). Adhesion molecules presence in diabetics without micro- or macro-vascular complications indicates that the endothelium is functioning, but is bound to release endothelial products, that are linked to microangiopathy development (26,27).

The levels of ICAM-1, VCAM-1, and HbA1c were shown to have a significant correlation in a recent study that measured glycemic control. Since prolonged uncontrolled hyperglycemia makes glycemic control more difficult, the levels of these molecules are greater when there is poor glycemic control (28). According to the findings of other studies, the levels of VCAM-1 in the isolated endothelial cells of diabetes patients are much greater than those of ICAM-1. This result is consistent with the concept that diabetics who have the consequences of their illness, such as macrovascular and diabetic renal disease, should have greater levels of VCAM-1 (29,30).

A recent study found that persons who had greater ICAM-1 and VCAM-1 showed higher TGs and lower HDL levels. Despite the importance of these molecules in the progression of atherosclerosis in diabetic and cardiovascular patients, studies indicated that the higher the levels of VCAM-1 and ICAM-1 the higher the risk of T2DM in individuals (31,32).

Conclusions:
VCAM-1 and ICAM-1 are potentially significant factors in the development of dyslipidemia in diabetes patients. They might serve as biomarkers to accurately predict the progression of cardiovascular disease.

Limitation: Insufficient sample size for statistical measurements and lack of previous research studies on the topic.

Authors' declaration:-
Conflicts of Interest: None
We hereby confirm that all Figures and Tables in this manuscript are ours. Besides, the figures and images, which are not ours, have been given permission for re-publication and attached to the manuscript.

Ethical Clearance: The institutional Scientific Committee at the National Diabetes Center/ Mustansiriya University approved this study according to the Declaration of Helsinki for human studies (Consent number: 1501 on 14/11/2022).

Author Contributions:

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دراسة جزيئات الإتصاص في المرضى العراقيين المصابين بداء السكري من النوع الثاني وارتفاع شحmites الدم

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المتصل: تم جمع السليم من المرضى والمصابين بداء السكري من النوع الثاني في مركز علاج القلب والأوعية الدموية في بغداد، وذلك خلال الفترة من أبريل 2019 إلى أبريل 2020.

كانت دراسة جزيئات الإتصاص في المرضى العراقيين المصابين بداء السكري من النوع الثاني وارتفاع شحمات الدم

الخلاصة:
-تم جمع السليم من المرضى والمصابين بداء السكري من النوع الثاني في مركز علاج القلب والأوعية الدموية في بغداد، وذلك خلال الفترة من أبريل 2019 إلى أبريل 2020.
-أظهرت النتائج أن هناك علاقة بين مستويات جزيئات الإتصاص ومستويات السليم عند المرضى والمصابين بداء السكري من النوع الثاني.
-تم قياس مستويات الـ VCAM-1 و ICAM-1 في المرضى والمصابين بداء السكري من النوع الثاني.
-أظهرت النتائج أن مستويات الـ VCAM-1 و ICAM-1 كانت أعلى في المرضى والمصابين بداء السكري من النوع الثاني مقارنة بمستويات السليم في المرضى السليمين.

Keywords:
- VCAM-1
- ICAM-1
- Type 2 Diabetes Mellitus
- Adhesion Molecules
- Baghdad

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How to Cite this Article

J Fac Med Baghdad

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Vol.66 No. 2, 2024