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Relationship between Status of Vitamin D and Adhesive Molecules Biomarkers in Saudi Patients with Type 2 Diabetes Mellitus

Abstract

Background: Vitamin D (25-OHD) has an essential protective action on vascular endothelium and endothelial dysfunction is a risk valuable marker for risk of cardiovascular disorders, which are common among patients with Type 2 diabetes mellitus (T2DM).

Objective: the aim of this study was to detect the link between level of vitamin D and adhesive molecules biomarkers in Saudi patients with type 2 diabetes mellitus.

Material and Methods: Two hundred Saudi patients with T2DM of both sexes (132 females and 68 males), their age range was 48-59 years, the diabetes chronicity range was 9-11 years and their body mass index (BMI) range was 31 to 37 Kg/m². All participants received oral hypoglycemic agents e.g. metformin and/or pioglitazone and were selected from the Internal Medicine Out-patient Clinic, King Abdulaziz Teaching Hospital, Jeddah, Saudi Arabia. Participants with respiratory failure, hepatitis, renal failure, heart failure, pregnancy and smokers excluded from the study. According to vitamin D level, participants were assigned to one of three groups: vitamin D deficiency group (A): 25-OHD <20 ng/ml, vitamin D insufficiency group (B): 25-OHD =20–30 ng/ml and normal vitamin D group (C) 25-OHD >30 ng/ml.

Results: The mean values of VCAM-1, ICAM-1 and E-selectin were significantly higher in vitamin D deficiency group (A) compared to vitamin D insufficiency group (B) and normal vitamin D group (C). Moreover, vitamin D showed a strong inverse relationship with VCAM-1, ICAM-1 and E-selectin in the three groups (P<0.05).

Conclusion: There is an association between vitamin D deficiency and abnormal levels of adhesive molecules biomarkers in Saudi patients with type 2 diabetes mellitus.

Keywords: Adhesive molecules; Endothelial Dysfunction; Type 2 Diabetes; Vitamin D

Introduction

Type 2 diabetes mellitus (T2DM) is a worldwide medical problem as 7-11% of world population have diabetes as reported by the International Diabetes Federation (IDF) in 2015 [1] and the number of T2DM patients is expected to reach 438 million by 2030 worldwide [2]. However, greater than 90% of this number is either overweight or obese [3]. Diabetes mellitus has a high impact on morbidity and mortality as diabetes mellitus associated with 2-4 fold risk for cardiovascular diseases and stroke in addition, diabetes is considered as a leading cause of renal disorders [4-6].

Endothelial dysfunction is known to predict cardiovascular future events in patients with T2DM [7,8] as endothelial dysfunction is an initial pathological change characterized by reduced vasodilation in vascular system. Moreover, endothelial dysfunction contributes in initiating and progressing of plaque which plays a principle role in pathogenesis of atherosclerosis [9] and arterial stiffness [10]. The biomarkers of endothelial cell activation molecules that commonly measured include intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and selectins (P and E-selectin), all of which are increased with endothelial dysfunction [11,12]. However, metabolic disorders commonly associated with chronic low grade of systemic inflammation and endothelial dysfunction [13,14]. Moreover, adequate intake of vitamin D (25-OHD) plays a protective role against systemic inflammation [15,16] in some conditions as obesity, T2DM and CVD [17-19].

Vitamin D has an important role in function of cardiovascular system [20,21], protective action for the vascular endothelium [22] and important role for kidney function [23]. Recently, deficiency of vitamin D is recognized as a public medical problem as it affects about 50% of population worldwide [24]. However, vitamin D deficiency raise the risk of microvascular diabetic complications in patients with T2DM [25,26].

As precise relationship between markers of endothelial function in T2DM subjects based on 25-OHD levels is still a matter of debate, therefore the aim of this study was to detect the link between level of vitamin D and adhesive molecules biomarkers in Saudi patients with type 2 diabetes mellitus.

Material and Methods

Subjects

Two hundred Saudi patients with T2DM of both sexes (132 females and 68 males), their age range was 48-59 years, the
diabetes chronicity range was 9-11 years and their body mass index (BMI) range was 31 to 37 Kg/m². All patients received oral hypoglycemic agents e.g., metformin and/or pioglitazone and were selected from the Internal Medicine Out-patient Clinic, King Abdulaziz Teaching Hospital, Jeddah, Saudi Arabia. Participants with respiratory failure, hepatitis, renal failure, heart failure, pregnancy and smokers excluded from the study. According to vitamin D level participants were assigned to one of three groups: vitamin D deficiency group (A): 25-OHD < 20 ng/ml, vitamin D insufficiency group (B): 25-OHD = 20–30 ng/ml and normal vitamin D group (C): 25-OHD > 30 ng/ml and all participants received no vitamin D supplementation. This study approved by the Ethical Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University.

**Measurements**

An overnight fasting blood samples were drawn from all participants for measurements of the following:

**A. Serum concentrations of 25-OH vitamin D:** Measurement of 25(OH) vitamin D for all patients and controls were done by the commercial kit RIA (Elisa Kit; DiaSorin, Stillwater, MN, USA). Plasma 25(OH) vitamin D concentrations of less than 20 ng/ml were defined as 25(OH) vitamin D deficiency and less than 30 ng/ml as 25(OH)D deficiency and insufficiency [27].

**B. Measurement of Adhesive molecules:** Level of inter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin were measured from frozen serum samples stored at −80°C using enzyme-linked immunosorbent assays (ELISAs) (R&D Systems, France).

**Statistical analysis**

SPSS (Chicago, IL, USA) version 23 was used for statistical analysis of data. Descriptive statistics for quantitative variables were presented as mean ± SD, while qualitative variables were presented as percentage and numbers. Analysis of variance (ANOVA) was used to compare between the three groups, P<0.05. While, Pearson's correlation coefficients (r) used to detect the degree of correlation between level of vitamin D and ICAM-1, VCAM-1 and E-selectin.

**Results**

Baseline characteristics of all participants who were assigned to one of three groups according to serum level of vitamin D into: vitamin D deficiency group (A): 25-OHD < 20 ng/ml, vitamin D insufficiency group (B): 25-OHD = 20–30 ng/ml and normal vitamin D group (C): 25-OHD > 30 ng/ml are presented in Table 1 and revealed no significant differences regarding all baseline criteria except fasting and postprandial blood sugar which were found to be significantly greater in group (A) than in group (B) and group (C) (Table 1).

The mean values of VCAM-1, ICAM-1 and E-selectin were significantly higher in vitamin D deficiency group (A) compared to vitamin D insufficiency group (B) and normal vitamin D group (C) (Table 2). Moreover, vitamin D showed a strong inverse relationship with VCAM-1, ICAM-1 and E-selectin in the three groups (Table 3) (P<0.05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group (C)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OHD Deficiency</td>
<td>51.74 ± 4.83</td>
<td>54.29 ± 3.97</td>
<td>52.86 ± 5.61</td>
<td>0.072</td>
</tr>
<tr>
<td>25-OHD Insufficiency</td>
<td>31.76 ± 3.24</td>
<td>32.15 ± 2.98</td>
<td>31.65 ± 3.47</td>
<td>0.023</td>
</tr>
<tr>
<td>25-OHD Normal</td>
<td>81.43 ± 26.51</td>
<td>151.36 ± 22.42</td>
<td>138.12 ± 18.13</td>
<td>0.012*</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>42(33%):85(67)</td>
<td>12(36%):21(64%)</td>
<td>14(352%): 26(65%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.36 ± 3.24</td>
<td>13.15 ± 2.98</td>
<td>13.65 ± 3.47</td>
<td>0.016*</td>
</tr>
<tr>
<td>Diabetes Duration (Year)</td>
<td>10.98 ± 3.72</td>
<td>12.43 ± 2.51</td>
<td>11.52 ± 2.97</td>
<td>0.025*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>134.21 ± 14.13</td>
<td>132.57 ± 12.84*</td>
<td>131.24 ± 12.75*</td>
<td>0.012*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>87.45 ± 6.16*</td>
<td>86.23 ± 5.78*</td>
<td>85.38 ± 5.91*</td>
<td>0.138</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; FBS: Fasting Blood Sugar; PPS: Postprandial Blood Sugar; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure (*) indicates a Significant Difference between Groups, P < 0.05.

**Table 2:** Comparison between the three groups concerning ICAM-1, VCAM-1 and E-selectin.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group (C)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OHD Deficiency</td>
<td>93.81±11.36</td>
<td>89.14±9.45</td>
<td>85.42±8.27</td>
<td>0.012*</td>
</tr>
<tr>
<td>25-OHD Insufficiency</td>
<td>815.92±35.51</td>
<td>784.63±32.38</td>
<td>761.53±29.12</td>
<td>0.016*</td>
</tr>
<tr>
<td>25-OHD Normal</td>
<td>16.11 ± 3.24</td>
<td>14.25 ± 2.71</td>
<td>12.16±2.46</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference between groups, P < 0.05.
**Discussion**

The blood vessels endothelium is the main source of circulating adhesive molecules which are the biomarkers of endothelial function [28,29]. Alteration in levels of adhesive molecules means endothelial dysfunction, which can be considered surrogates for high cardiovascular disorders (CVD) risk [30]. However, there still contradicted data regarding the association between level of vitamin D and endothelial dysfunction in patients with T2DM. Therefore, the aim of this study was to detect the link between level of vitamin D and adhesive molecules biomarkers in Saudi patients with type 2 diabetes mellitus.

Our results revealed that the mean values of VCAM-1, ICAM-1 and E-selectin were significantly higher in vitamin D deficiency group (A) compared to vitamin D insufficiency group (B) and normal vitamin D group (C). Moreover, vitamin D showed a strong inverse relationship with VCAM-1, ICAM-1 and E-selectin in the three groups. These findings are consistent with several previous observational studies reported an associations between endothelial dysfunction and low levels of circulating vitamin D in health subjects as Tarcin et al. [31] found among 23 asymptomatic individuals, there was an association between impaired brachial artery FMD of T2DM patients significantly improved after single dose of vitamin D (100,000 IU) for 2 months. Similarily, Jablonski & Yi et al. [32,33] found a negative relationship between inflammatory cytokines, endothelial dysfunction recorded by brachial artery FMD and level of vitamin D in adult subjects. However, Harris et al. [34] stated 16 weeks of supplemental high dose of vitamin D (60,000 IU /month) significantly improved endothelial function that measured by FMD. While, Al Mheid & Dong et al. [35,36] found improvement in vascular dysfunction in healthy subjects as evident by reduction in mean arterial pressure after supplement of vitamin D.

In the other hand, changes in level of vitamin D can influence endothelial function in pathological conditions as evident by Yiu & colleagues [33] who stated that deficiency of vitamin D was associated with endothelial dysfunction documented by FMD in 280 patients with T2DM. In addition, Sugden et al. [37] reported that brachial artery FMD of T2DM patients significantly improved after single dose of vitamin D (100,000 IU) for 2 months. Moreover, Codoner-Franch et al. [35] proved that level of vitamin D was linked to systemic inflammation, oxidative stress and VCAM-1 levels in 66 obese children. There are several possible mechanisms for the link between vitamin D and endothelial function included reduction of blood pressure due to suppression of renin-angiotensin system [39], reduction of vascular resistance [40], modulation of inflammatory cytokines effects on blood vessels [41], reduction of adhesive molecules, reduction of platelet aggregation [42] and finally through reduction of oxidative stress [43].

**Conclusion**

There is an association between vitamin D deficiency and abnormal levels of adhesive molecules biomarkers in Saudi patients with type 2 diabetes mellitus.

**Acknowledgement**

The author thanks Prof. Osama H. Al-Jiffri for his skillful assistance in selection of participants, laboratory analysis and during clamp procedures of this study. In addition, author is grateful for the cooperation and support of all patients who participated in this study.

**Conflict of Interest**

None.

**References**


**Table 3:** Correlation coefficient (r) of vitamin D and ICAM-1, VCAM-1 & E-selectin in the three groups.

<table>
<thead>
<tr>
<th></th>
<th>Group (A)</th>
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<th>Group (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-OHD Deficiency</td>
<td>25-OHD Insufficiency</td>
<td>25-OHD Normal</td>
</tr>
<tr>
<td>ICAM-1 (ng/ml)</td>
<td>-0.681**</td>
<td>-0.531*</td>
<td>-0.647**</td>
</tr>
<tr>
<td>VCAM-1 (ng/ml)</td>
<td>-0.719**</td>
<td>-0.634**</td>
<td>-0.648**</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>-0.547*</td>
<td>-0.625**</td>
<td>-0.512*</td>
</tr>
</tbody>
</table>

Spearman’s correlation was used *: P < 0.05 **: P < 0.01


