Austin Journal of Clinical Immunology

Open Access

Austin Publishing Group

Review Article

Deficiency of Vitamin D, Immune System Function and Glucose Control in Non-Insulin Dependent Diabetic Patients

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Received: January 17, 2019; **Accepted:** February 21, 2019; **Published:** February 28, 2019

Abstract

Background: Recently, Vitamin D (25-OHD) deficiency is a global pandemic medical problem, which usually associated with high risk of osteoporosis, Non-Insulin Dependent Diabetes Mellitus (NIDDM), different types of cancer, autoimmune and cardiovascular disorders.

Objective: This study designed to measure the association between Vitamin D deficiency, immune system function and glucose control in non-insulin dependent diabetic patients. Material and Methods: Two hundred fifty seven non-insulin dependent diabetic Saudi patients (163 females and 94 males), treated with oral hypoglycemic medications (e.g. pioglitazone and/or metformin), their chronicity of diabetes was 11.68±2.97 years, the mean of their Body Mass Index (BMI) was 32.51±2.94 kg/m^2. However, smokers, pregnant women and patients with hepatic, renal, respiratory and heart failure were excluded. According to the level of 25-OHD levels, participants were enrolled in 3 groups: Vitamin D deficiency group (I) with 25-OHD less than 20 ng/ml (Vitamin D deficiency), group (II) with 25-OHD =20–30 ng/ml (Vitamin D insufficiency) and group (III) with 25-OHD greater than 30 ng/ml (normal Vitamin D).

Results: Concerning parameters of blood glucose control, results revealed higher significant values of the Quantitative Insulin-Sensitivity Check Index (QUICKI) in group (III) compared to group (II) and group (I) in addition to lower values of both Homeostasis Model Assessment (HOMA-IR) and glycosylated hemoglobin (HBA1c) in group (III) compared to group (II) and group (I). However, parameters of immune system results revealed higher significant values of the number of white blood cells, monocytes, total neutrophil count, CD3, CD4 and CD8 in group (I) compared to group (II) and group (III) ($P<0.05$). However, there was a strong inverse relationship between 25-OHD & HOM-IR, HBA1c, WBCs, total neutrophil, monocytes, CD3, CD4 and CD8 count in addition to a strong direct relationship between 25-OHD & QUICKI in the three groups ($P<0.05$).

Conclusion: This study provides evidence that Vitamin D deficiency adversely affects immune system and glucose control among non-insulin dependent diabetic patients.

Keywords: Glucose control; Immune system; Non-insulin dependent diabetes; Vitamin D

Introduction

Vitamin D (25-OHD) deficiency is global medical problem specially in Middle east and Asia [1]. Many studies confirmed the association between status of 25-OHD with cardiovascular diseases and diabetes-related out-comes [2-7] as there was a negative relation between diabetes prevalence and status of Vitamin D [8,9].

Insulin resistance and systemic inflammation are usually associated with diabetes [10], therefore 25-OHD improves islet-cell functions and as a result reduces insulin resistance and its anti-inflammatory action [11-14] that means 25-OHD deficiency facilitates development of diabetes and reduce responses to medications [15-18].

Vitamin D is important for many physiological processes regulation as homeostasis of calcium, muscle and bone health [19]. Therefore, this study aimed to measure the association between 25-OHD deficiency, immune system function and glucose control in patients with NIDDM.

Material and Methods

Subjects

Two hundred fifty seven NIDDM Saudi patients (164 females and 93 males), treated with oral hypoglycemic medications (e.g. pioglitazone and/or metformin), their chronicity of diabetes was 11.25±4.73 years, the mean of their Body Mass Index (BMI) was 32.86±2.94 kg/m^2. However, smokers, pregnant women and patients with hepatic, renal, respiratory and heart failure were excluded. According to the level of 25-OHD levels, participants were enrolled

Citation: Al-Shred FM. Deficiency of Vitamin D, Immune System Function and Glucose Control in Non-Insulin Dependent Diabetic Patients. Austin J Clin Immunol. 2019; 6(1):1034.

Table 1: Baseline criteria for participants of the three groups.

Variables	Group (I)	Group (II)	Group (III)	Significance
Age (year)	53.25 ± 5.37	54.36 ± 7.94	51.81 ± 6.12	0.16
Gender (Female: Male)	102(62%):61(38%)	33(65%):18(35%)	29(68%):14(32%)	0.081
BMI (kg/m^2)	31.98 ± 3.67	32.72 ± 2.85	32.64 ± 2.31	0.172
Waist hip ratio	0.87 ± 0.18	0.88 ± 0.21	0.88 ± 0.19	0.215
Chronicity of diabetes (year)	11.74 ± 3.83	10.95 ± 2.14	12.36 ± 3.25	0.079
Fasting blood sugar (mg/dL)	177.36 ± 31.72	151.53 ± 22.67	128.12 ± 16.84	0.011*
Postprandial blood sugar (mg/dl)	268.17 ± 42.65	197.56 ± 33.24	172.35 ± 20.91	0.005*
Insulin (mU/L)	15.81 ± 2.87	14.12 ± 2.93	12.41 ± 2.15	0.024*

BMI: Body Mass Index; (*) indicates a significant difference between groups, P <0.05.

Table 2: Comparison between Patients' groups regarding WBCs, total neutrophil, monocytes, CD3, CD4 , CD8 count, serum insulin, QUICKI, HBA1c and HOM-IR.

Variable	Group (I)	Group (II)	Group (III)	Significance
WBCs count (10^9/μL)	9.47 ±3.28	7.95 ± 3.16	6.13 ± 2.45	0.012*
Total neutrophil count (10^9/μL)	6.32 ± 2.54	5.14 ± 2.27	4.25 ± 1.98	0.005*
Monocytes (10^9/μL)	0.67 ± 0.26	0.49 ± 0.24	0.31 ± 0.17	0.031*
CD3 count (10^9/L)	1.95 ±0.83	1.63 ± 0.84	1.36 ± 0.65	0.016*
CD4 count (10^9/L)	1.57 ± 0.72	1.41 ± 0.65	1.19 ± 0.52	0.029*
CD8 count (10^9/L)	0.89 ± 0.26	0.74 ± 0.23	0.53 ± 0.18	0.042*
HBA1c (%)	9.41 ± 3.12	8.15 ± 2.34	7.24 ±2.85	0.011*
HOMA-IR	5.78 ±1.85	4.23 ±1.61	3.97 ± 1.42	0.015*
QUICKI	0.119 ±0.06	0.155 ± 0.08	0.186 ±0.09	0.022*

WBCs: White Blood Cells; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) Index; HBA1c: Glycosylated Hemoglobin; QUICKI: The Quantitative Insulin-Sensitivity Check Index; (*) indicates a significant difference between groups, P <0.05.

in 3 groups: group (I) with 25-OHD less than 20 ng/ml (Vitamin D deficiency), group (II) with 25-OHD=20-30 ng/ml (Vitamin D insufficiency) and group (III) with 25-OHD greater than 30 ng/ml (normal Vitamin D). All participants signed informed consent before sharing in this study.

Measurements

A. Measurement of 25-hydroxyVitamin D (25-OHD) was undertaken using the commercial kit RIA (Elisa Kit; DiaSorin, Stillwater, MN, USA) [20,21].

B. Immune system parameters (CD3, CD4 and CD8): Flow cytometry using Cytomics FC500 and CXP software (Beckman Coulter) was used to measure the leukocyte differentiation antigens CD3, CD4 and CD8 (Beckman Coulter, Marseille, France). However, Beckman Coulter AcT 5diff hematology analyzer was used in analysis of peripheral blood cells (The number of white blood cells (WBCs), total neutrophil count and monocytes).

C. Serum glucose control: Concentration of plasma insulin and glucose undertaken using the commercial available kits (Roche Diagnostics GmbH, Mannheim, Germany). However, insulin resistance was detected using homeostasis model assessment (HOMA-IR). HOMA-IR = [fasting blood glucose (mmol/l)-fasting insulin (mIU/ml)]/22.5 [22]. Moreover, The Quantitative Insulin-Sensitivity Check Index (QUICKI) was the insulin sensitivity test using the formula: QUICKI=1/[log(insulin) + log(glucose)] [23].

Statistical analysis

All variables were analyzed using SPSS version 17(Chicago, IL, USA) and described as mean ± SD. However, ANOVA was used for comparing variables between the three groups. Moreover, Pearson's correlation coefficients was used for testing correlation between 25-OHD, HBA1c, QUICKI, serum insulin, HOM-IR, the number of WBCs, total neutrophil count and monocytes (P<0.05).

Results

Comparison between the three groups regarding baseline variables revealed no significant differences except values of fasting and postprandial blood sugar levels were significantly greater in group (I) than both group (II) and group (III) (Table 1).

Concerning parameters of blood glucose control, results revealed higher significant values of QUICKI in group (III) compared to group (II) and group (I) in addition to lower values of both HBA1c and HOM-IR in group (III) compared to group (II) and group (I). However, parameters of immune system results revealed higher significant values of the number of WBCs, monocytes, total neutrophil count, CD3, CD4 and CD8 in group (I) compared to group (II) and group (III) (Table 2).

The Pearson's correlation coefficients test showed that there was a strong inverse relationship between 25-OHD & HOM-IR, HBA1c, WBCs, total neutrophil, monocytes, CD3, CD4 and CD8 count in addition to a strong direct relationship between 25-OHD & QUICKI in the three groups (Table 3) (P<0.05).

Discussion

Vitamin D deficiency is worldwide pandemic [24]. However, there

Table 3: Correlation coefficient (r) of 25-OHD & QUICKI, HOM-IR, HBA1c, WBCs, total neutrophil, monocytes, CD3, CD4 and CD8 count in the three groups.

Variable	Group (I)	Group (II)	Group (III)
WBCs count (10^9/μL)	-0.681**	-0.573*	-0.614*
Total neutrophil count (10^9/μL)	-0.537*	-0.638*	-0.642*
Monocytes (10^9/μL)	-0.732**	-0.663*	-0.519*
CD3 count (10^9/L)	-0.651*	-0.592*	-0.711**
CD4 count (10^9/L)	-0.583*	-0.675**	-0.634*
CD8 count (10^9/L)	-0.672**	-0.723**	-0.586*
HBA1c (%)	-0.684**	-0.618*	-0.734**
HOMA-IR	-0.756**	-0.724**	-0.567*
QUICKI	0.691**	0.638*	0.718**

WBCs: White Blood Cells; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) Index; HBA1c: Glycosylated Hemoglobin; QUICKI: The Quantitative Insulin-Sensitivity Check Index; Spearman's correlation was used*: P <0.05 **: P <0.01

is evidence that 25-OHD has a role in regulation of innate immune system [25] in addition to influence pathogenesis of several disorders as cancer, infections, autoimmune diseases, psychiatric disorders, diabetes mellitus [26,27]. We found a significant negative association between level of 25-OHD and serum insulin, HbA1c and HOMA-IR, in addition to positive association between level of 25-OHD and The Quantitative Insulin-Sensitivity Check Index (QUICKI), these results in harmony with many previous studies which reported an inverse association between glucose intolerance and 25-OHD level among patients with non-insulin dependent diabetes or metabolic syndrome [28-31]. In animal models, deficiency in 25-OHD inhibited insulin secretion and induced glucose intolerance [32,33]. However, several authors reported direct relation between level of 25-OHD and insulin sensitivity [34-36]. Similarly, Pirgon and colleagues reported negative relation between HOMA-IR and level of 25-OHD among obese patients with non-alcoholic fatty liver [37]. In addition, Alissa and coworkers reported a negative association between 25-OHD and fasting blood glucose among 300 postmenopausal Saudi women [38].

In the other hand, Elseweidy and colleagues reported that supplementation of 25-OHD improved insulin sensitivity in diabetic rat [39]. However, Pittas et al. proved that insulin resistance improved following three years of calcium-Vitamin D supplements among 314 nondiabetic adult subjects [40]. Moreover, Calvo-Romero and Ramiro-Lozano reported that 28 patients with non-insulin dependent diabetes mellitus received 16,000 IU of 25-OHD supplementation for 48 days and had improved QUICKI and HOMA-IR [41]. Similarly, Osati et al. stated that 2 months of supplemental 25-OHD improved measures of serum insulin and insulin sensitivity among 210 individuals with 25-OHD deficiency [42]. While, the results of meta-analysis conducted by Jamka and colleagues which only seven studies out of 11 clinical trials proved that included 1181 obese and overweight subjects had reduction in blood glucose, insulin and HOMA-IR following 25-OHD supplementation [43]. The improved glucose control following Vitamin D supplementation may be was due to the anti-inflammatory activity of 25-OHD that inhibit release of inflammatory cytokines and improved expression of insulin receptor [44], another mechanism Vitamin D modulates level Parathyroid Hormone (PTH) as increased level of PTH impair insulin sensitivity [45].

Concerning immune system parameters, non-insulin dependent diabetic patients with 25-OHD deficiency had significantly increased mean of the WBCs number, total neutrophil count, monocytes, CD3, CD4 and CD8 than non-insulin dependent diabetic patients with normal 25-OHD was an strong inverse relationship between 25-OHD and white blood cells, total neutrophil count, monocytes, CD3, CD4, and CD8 in all groups. Our findings agreed with the findings of several previous studies as Nnoaham and Clarke who completed a meta-analysis and proved that risk of active tuberculosis is directly associated with 25-OHD deficiency [46]. While, Zaki et al. conducted a study that included 201 obese Egyptian women with Vitamin D deficiency and reported that abnormal level of inflammatory cytokines and insulin resistance are associated with 25-OHD deficiency, in addition they stated that Vitamin D Receptor (VDR) gene polymorphisms has an important role in immune system and systemic inflammation status [47]. However, Cannell and colleagues stated that level of Vitamin D affects the risk for upper respiratory tract infection as influenza [48]. In the other hand, Urashima et al. approved that administration of supplemental 25-OHD led to significant reduction in the incidence of schoolchildren influenza A [49]. Moreover, Camargo et al. reported that three months of 25(OH)D supplementation significantly lowered the risk of winter acute respiratory infections in their randomized controlled study that included 247 severely 25-OHD deficient Mongolian schoolchildren [50]. Similarly, Bergman and colleagues confirmed that a randomized controlled study that enrolled 140 Swedish immune-deficient patients who received supplemental 25-OHD for one year gained significant reduction in their infectious symptoms and frequency of respiratory tract infections [51]. The immune system response following 25-OHD supplementation may be due to activation of enzymes in B and T cells through expression of Vitamin D Receptors (VDR) that influence proliferation and differentiation of T and B cells [52-55].

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Austin J Clin Immunol - Volume 6 Issue 1 - 2019
ISSN : 2381-9138 | www.austinpublishinggroup.com

Citation: Al-Shred FM. Deficiency of Vitamin D, Immune System Function and Glucose Control in Non-Insulin Dependent Diabetic Patients. Austin J Clin Immunol. 2019; 6(1):1034.