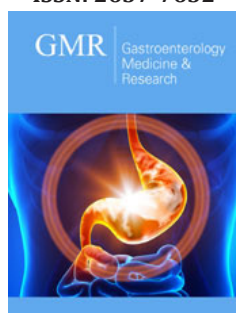


Relation between 25-Hydroxyvitamin D, Systemic Inflammation and Endothelial Function Biomarkers in Diabetic Nephropathy

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Abstract

Background: Diabetic nephropathy (DN) is a microvascular diabetic complications that leads to renal failure worldwide. However, vitamin D is essential to maintain health of vascular system.

Objective: The target of this study was to measure the association between 25-hydroxyvitamin D, systemic inflammation and endothelial function biomarkers in patients with type 2 diabetic nephropathy.

Material and Methods: Two hundred Saudi obese type 2 diabetes mellitus (T2DM) patients (114 males and 86 females), their body mass index (BMI) was 31-35Kg/m² and the chronicity of diabetes was 11.87±2.95 year enrolled in the present study. Smokers and patients with renal insufficiency, congestive heart failure, pregnancy, respiratory failure and hepatitis were excluded. Participants were enrolled into three equal groups: group (A) 25-OHD<20ng/ml (deficiency of vitamin D), group (B): 25-OHD=20-30 ng/ml (insufficiency of vitamin D) and group(C) 25-OHD >30ng/ml (normal vitamin D). Consent from was signed by participants.

Results: Mean values of VCAM-1, ICAM-1, E-selectin, TNF- α , IL-6 and CRP were significantly greater in group(A) compared to group(B) and group(C). However, vitamin D showed a strong inverse relationship with these parameters in the three groups (P<0.05).

Conclusion: Level of vitamin D closely related to systemic inflammation and endothelial function biomarkers in Saudi patients with diabetic nephropathy

Keywords: Inflammatory cytokines; Diabetic nephropathy; Endothelial dysfunction; Vitamin D

Introduction

Diabetic nephropathy (DN) is a common metabolic disorder with progressive rate of morbidity and mortality worldwide [1]. However, DN is a global diabetic microvascular complication leads to renal failure [2-5]. While, DN occur in 20-40% of type 2 diabetes mellitus (T2DM) patients and the principal etiology of renal failure [6,7]. Patients with DN suffer from high rate of morbidity and mortality. In fact, a rapid kidney function decline is a predictor for both cardiovascular disorders as well as all-cause mortality [8-10]. Risk factors of DN include poor metabolic control, diabetes duration, race, heredity, lifestyle, diet composition, aging and hypertension. On the other hand, systemic inflammation and endothelial dysfunction are 2 serious elements in promoting DN [11-13]. Vitamin D is essential for the function and health of the heart, blood vessels and kidney [14-17]. However, deficiency of vitamin D affects about 50% of worldwide population and induce many vascular complications among T2DM patients [18-20]. Therefore, this study aimed to detect the association between vitamin D, systemic inflammation and endothelial function biomarkers in patients with T2DM nephropathy.

Material and Methods

Subjects

Two hundred Saudi obese type 2 diabetes mellitus (T2DM) patients (114 males and 86 females), their body mass index (BMI) was 31-35Kg/m² and the chronicity of diabetes was 11.87±2.95 year enrolled in the present study. Smoking, cancer, immune system disorders and pain, antidepressant, anti-inflammatory medications were the exclusion criteria. Participants were enrolled into three equal groups: group(A) 25-OHD<20ng/ml (deficiency of vitamin D), group(B): 25-OHD=20-30ng/ml (insufficiency of vitamin D) and group(C) 25-OHD>30ng/ml (normal vitamin D). Consent from was signed by participants.

Measurements

- A. Level of 25-hydroxyvitamin D (25-OHD) serum measurements:** Overnight fasting venous blood sample was drained and was centrifuged to measure 25(OH) vitamin D for all participants. RIA (Elisa Kit; DiaSorin, Stillwater, MN, USA) was the commercial kit to measure 25(OH) vitamin D. Normal level of vitamin D is >30ng/ml, while level of <20ng/ml is considered as vitamin D deficiency.
- B. Measurement of Adhesive molecules:** Enzyme-linked immunosorbent assays (ELISAs) (R&D Systems, France) were used to measure values of inter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin.
- C. Inflammatory cytokines measurements:** TNF- α and IL-6 were measured using (GE Healthcare Amersham, Biotrak Easy ELISA). While, enzymatic-colorimetric method with kits (Roche Diagnostics, Mannheim, Germany) were used to measure C-reactive protein (CRP).

Statistical analysis

SPSS (Chicago, IL, USA) version 23 was used for statistical analysis of data. Descriptive statistics for quantitative variables were presented as mean \pm 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 VCAM-1, ICAM-1, E-selectin, TNF- α , IL-6 & CRP.

Results

Participants baseline criteria of the three groups presented in (Table 1). Mean values of HDL-c, LDL-c, TC, TG, HbA1C and Creatinine revealed significant differences among the three groups. While, mean values of age and BMI revealed no significant differences among the three groups (Table 1). Mean values of VCAM-1, ICAM-1, E-selectin, TNF- α , IL-6 and CRP were significantly greater 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 these parameters in the three groups (Table 3) ($P < 0.05$).

Table 1: Participants baseline criteria. BMI-Body mass index; HDL-c-High-density lipoprotein cholesterol; LDL-c-Low-density lipoprotein cholesterol; TG-Triglyceride; TC-Total cholesterol ; HbA1C-Glycosylated hemoglobin ; (*)-indicates a significant difference between groups, $P < 0.05$.

Variable	Group (A) 25-OHD Deficiency	Group (B) 25-OHD Insufficiency	Group (C) 25-OHD Normal	Significance
Age (year)	49.84 \pm 5.13	51.32 \pm 5.25	50.62 \pm 4.38	$P < 0.05$
BMI (kg/m ²)	32.36 \pm 4.32	30.78 \pm 4.56	31.93 \pm 4.14	$P < 0.05$
HDL-c (mg/dl)	31.57 \pm 5.28*	34.21 \pm 5.61	39.69 \pm 6.37	$P < 0.05$
LDL-c (mg/dl)	178.24 \pm 26.49*	162.36 \pm 21.27	115.49 \pm 18.65	$P < 0.05$
TC (mg/dl)	257.31 \pm 38.16*	228.53 \pm 31.35	195.42 \pm 24.82	$P < 0.05$
TG (mg/dl)	235.25 \pm 35.74*	214.42 \pm 28.12	168.38 \pm 21.35	$P < 0.05$
HbA1C (%)	8.57 \pm 1.43*	7.13 \pm 1.21	4.97 \pm 0.86	$P < 0.05$
Creatinine (μ mol/mol)	86.35 \pm 10.72*	79.26 \pm 8.68	68.13 \pm 6.27	$P < 0.05$

Table 2: Comparison between the three groups concerning VCAM-1, ICAM-1, E-selectin, TNF- α , IL-6 & CRP.

Variable	Group (A) 25-OHD Deficiency	Group (B) 25-OHD Insufficiency	Group (C) 25-OHD Normal	Significance
Creatinine (μ mol/mol)	85.36 \pm 9.45*	79.24 \pm 8.32	71.38 \pm 7.26	$P < 0.05$
ICAM-1 (ng/ml)	91.72 \pm 10.11*	87.35 \pm 9.25	82.52 \pm 8.17	$P < 0.05$
VCAM-1 (ng/ml)	803.13 \pm 31.24*	775.24 \pm 28.71	757.38 \pm 26.39	$P < 0.05$
E-selectin (ng/ml)	15.21 \pm 3.87*	13.11 \pm 2.95	11.29 \pm 2.56	$P < 0.05$
TNF- α (pg/mL)	10.62 \pm 3.25*	9.37 \pm 2.86	7.28 \pm 2.23	$P < 0.05$
IL-6 (pg/mL)	6.14 \pm 1.54*	4.43 \pm 1.21	3.65 \pm 1.15	$P < 0.05$
CRP (mg/L)	4.67 \pm 1.39*	3.11 \pm 1.24	2.27 \pm 1.12	$P < 0.05$

ICAM-1-Inter-cellular adhesion molecule; VCAM-1-Vascular cell adhesion molecule; TNF- α -Tumor necrosis factor- α ; IL-6-Interleukin-6; CRP-C-reactive protein; (*)-indicates a significant difference between groups, $P < 0.05$.

Table 3: Correlation coefficient (r) of vitamin D and VCAM-1, ICAM-1, E-selectin, TNF- α , IL-6 & CRP in the three groups. Spearman's correlation was used*: P<0.05**: P<0.01.

Variable	Group (A) 25-OHD Deficiency	Group (B) 25-OHD Insufficiency	Group (C) 25-OHD Normal
Creatinine ($\mu\text{mol/mol}$)	-0.742**	-0.675*	-0.624**
ICAM-1 (ng/ml)	-0.564*	-0.542*	-0.617*
VCAM-1 (ng/ml)	-0.682**	-0.657**	-0.521*
E-selectin (ng/ml)	-0.631*	-0.743**	-0.672**
TNF- α (pg/mL)	0.728**	0.612*	0.543*
IL-6 (pg/mL)	0.654*	0.585*	0.641**
CRP (mg/L)	0.591*	0.614**	0.527*

Discussion

Diabetic nephropathy (DN) considered as the most serious T2DM complication [21,22]. While, vitamin D deficiency among T2DM patients is common [23]. Vitamin D share in regulation of insulin sensitivity and secretion and ameliorates systemic inflammation [24]. Limited information is available about relation between cardiovascular dysfunction and D deficiency among DN patients [25,26]. Therefore, this study aimed to detect the association between vitamin D, systemic inflammation and endothelial function among T2DM patients nephropathy.

Results of this study indicated that vitamin D deficiency group (A) had greater significant mean values of TNF- α , IL-6 and CRP than group (B) and group (C) in addition to a negative relation between these systemic inflammatory parameters and vitamin D level. These findings agreed with many previous studies [27,28]. Moreover, several researches proved that vitamin D deficiency related to higher inflammatory cytokines levels [29-32]. In the other hand, many previous trails on different pathological conditions stated that administration of supplemental vitamin D for different durations resulted in highly significant down regulation of inflammatory cytokines which prove the ameliorating effect of vitamin D upon the systemic inflammation [33-35].

Concerning results of endothelial function parameters, vitamin D deficiency group (A) had greater significant mean values of VCAM-1, ICAM-1 and E-selectin than group (B) and group (C) in addition to a inverse relation between these parameters and vitamin D level. These findings approved by proved that low vitamin D was related to endothelial dysfunction [36-38]. In the other hand, many previous trails on different pathological conditions stated that administration of supplemental vitamin D for different durations resulted in highly significant improvement in endothelial function [39-43]. Renin-angiotensin system inhibition [44], vascular resistance reduction [45], inflammatory cytokines amelioration [46] and reduction of platelet aggregation [47-49] & oxidative stress are the mechanisms that link of vitamin D and endothelial function.

Conclusion

Level of vitamin D closely related to systemic inflammation and endothelial function biomarkers in Saudi patients with diabetic nephropathy.

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