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The Association of 25(OH) Vitamin D Level with Glycemic Control and Nephropathy Complication in Sudanese with Type 2 Diabetes

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ABSTRACT

Background: *Diabetic nephropathy is principle cause of end stage kidney failure worldwide. Numerous research studies documented that 25(OH) vitamin D has numerous extra skeletal effects including glycemic control and diabetic nephropathy complication.* ***Objectives:*** *To compare the level of 25(OH) vitamin D between Type 2 diabetic patients with and without nephropathy complication and healthy subjects, and to assess the relationship between 25(OH) vitamin D level with glycemic control and nephropathy complication.* ***Materials and Methods:*** *This is cross-sectional case control study conducted on 40 diabetics with nephropathy complication, 40 control diabetics without nephropathy complication and 40 control healthy subjects, were compared in term of 25(OH) vitamin D, HbA, microalbumin, FBS and C-peptide.* ***Results:*** *There is significant decrease in the mean of serum 25(OH) vitamin D (11.5 ± 3.4 versus 20.4 ± 3.1, p ≤ 0.00) and C-peptide (1.14 ± 0.2 versus 2.23 ± 0.23, p=0.00), with significant increase in HbA1c (10.4 ± 1.6 versus 8.5 ± 1.2, p ≤ 0.00) microalbumin (144.5 ± 16.3 versus 8.5 ± 1.3, p ≤ 0.00), FBS (206.4 ± 32.9 versus 182.9 ± 29.1, p ≤ 0. 01) in the study group when compared with their control group. According to serum 25(OH) vitamin D levels, HbA1c, microalbumin and FBG levels were significantly elevated in patient with deficiency 25(OH) vitamin D level than in patients with insufficiency level (p ≤ 0.05) in the study group. The study recorded significant negative correlation between serum 25-OH vitamin D level with disease duration, (r=0.333, p=0.00) and FBG (r= -0.43, p=0.01) with insignificant correlation with age, (r=0.025, p=0.405) and c-peptide (r= -0.12, p=0.54). Also, serum 25(OH) vitamin D level is inversely correlated with HbA1c (r= -0.37, p=0.03), and microalbumin (r= -0.29, p=0.05) in diabetic patient with nephropathy complication.* ***Conclusion:*** *The study demonstrated that low 25(OH) Vitamin D level is inversely correlated with glycemic control and nephropathy complication in Type 2 Diabetes. Vitamin D supplementation benefits for glycemic control and prevention of nephropathy in type 2 diabetes.*

Keywords: Type 2 diabetes mellitus, 25(OH) vitamin D, Nephropathy, HbA1c, Microalbumin

INTRODUCTION

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) and transplantation worldwide; 46% of patients with type 1 DM and 10% to 30% of patients with type 2 diabetes develop microalbuminuria, proteinuria, and ESRD secondary to diabetes [1]. Diabetic nephropathy is a clinical syndrome characterized by albuminuria (>300 mg/day or >200 mcg/min), permanent irreversible decrease in glomerular filtration rate (GFR), and arterial hypertension [2]. Nephropathy is a chronic complication of both type 1 DM and type 2 DM [3]. Albuminuria remains the only biomarker acceptable for diagnostic purposes, although some growth factors are expected to replace albuminuria in future [4]. The prognostic value of a small amount of albumin in urine marker of progression of kidney damage in patients with type 1 or 2 DM was confirmed in the early 1980's. This stage of kidney damage was called the microalbuminuria stage or initial nephropathy [5]. Glomerular filtration barrier functions as a complex biological

sieve. As opposed to other capillaries in the body, glomerular capillaries are highly permeable to water and relatively impermeable to large molecules [5-7]. Pathological changes develop in the glomeruli of patients with long-duration DM before the appearance of microalbuminuria [6-8]. The severity of glomerular damage is proportional to GFR value, DM duration, and blood glucose regulation [6,7]. The main pathohistological changes in diabetic nephropathy include the thickening of the glomerular basement membrane (GBM), mesangial expansion, nodular sclerosis - Kimmelstiel-Wilson change, diffuse glomerular sclerosis, tubular interstitial fibrosis, and arteriosclerosis and renal arteriolar hyalinosis [7,8].

The main sources of vitamin D are sunlight, supplements, and diet [9] 25-hydroxyvitamin D (25(OH)D) is the major circulating form of vitamin D [9,10]. The preferred healthful range is 30-60 ng/mL) [9]. It is biologically inactive and converted in the kidneys by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to its active form 1,25-dihydroxyvitamin D (1,25(OH)2D) [9-11]. Vitamin D is transported to the fat where it can be storage or to the liver for activation, the hydroxylation to 25-hydroxyvitamin D (25(OH)D) is measured to assess a patient's vitamin D status [12-14]. In addition to its traditional role in calcium and phosphate hemostasis [15-17]. Recently, vitamin D has acquired large interest in the pathogenesis and prevention of diabetes [15,16]. As the major regulator for calcium homeostasis, vitamin D directly and or indirectly improves insulin exocytosis via activating calcium-dependent endopeptidases. Vitamin D also improves glucose tolerance [15-17]. Vitamin D could also prevent type 2 diabetes through its role as an efficient antioxidant [16,17]. Additionally, the steroid hormone form of vitamin D promotes suppressor cell activity and inhibits the generation of cytotoxic [16,17].

The role of the kidney in the hydroxylation of the vitamin D to the biologically active form $1,25(OH)_2D_3$ is well established [15,16]. Animal studies suggest that, in addition to chronic renal failure has on increasing the likelihood of $1,25(OH)_2D_3$ deficiency and insufficiency caused by the kidneys, vitamin D deficiency and insufficiency also have an active role in the progression of kidney disease [9]. This study targets to investigates a possible relation- ship between vitamin D status, with glycemic control and nephropathy in Sudanese patients with type 2 diabetes.

PATIENTS AND METHODS

This is cross-sectional case control hospital base study was conducted at Jaber Abu Eliz Diabetes Center. Khartoum state during the period February 2015 to April 2016. The protocol of this study was approved by Alneelain university ethics committee and Informed consent was obtained from each patient. A total of 80 patients with type 2 diabetes mellitus were enrolled, of which 40 with nephropathy complication and 40 without nephropathy complication. In addition to 40 control healthy subjects.

Inclusion Criteria

Sudanese patients with type 2 diabetes mellitus who visited Jabir Abu Eliz diabetic center during the study period.

Exclusion Criteria

Patients with clinical history of renal disease from other cause than diabetes, end stage renal disease, hypertension, cancer, autoimmune disorders, recent liver disorder, patient in supplementation on vitamin D and pregnant women were excluded from this study.

Data Collection and Clinical Examination

An interview with a questionnaire to obtain the clinical and demographic data was used for each participant in this study. Clinical history and examination of the test group and the control group were done by a physician to help the classification of study group. For a diagnosis of nephropathy, patients were defined as having microalbuminuria with spot urine sample albumin content of 30-300 mg/L.

Sample Collection

After obtaining informed consent, sample from the participants were collected. Spot urine samples (mid-stream) were collected in a sterile clean urine container for microalbumin determination. Venous blood (5 ml) was withdrawn after overnight fasting from patients by standard procedures by using a vacationer tube. The blood was divided into two containers; 2 ml of blood was collected in sodium fluoride for the determination of fasting blood sugar and HbA1c. HbA1C was estimated at the same time of collection then the tubes were centrifuged for 10 minutes at 3000 rpm, and the plasma was separated in a plain container and used for analysis of fasting blood Glucose. The rest 3 ml of blood were collected in lithium heparin container, centrifuged (3000 rpm) for 10 minutes, and plasma was used for estimation of C-peptide and 25-OH vitamin D.

Biochemical Measurements

Microalbumin was determined by using a fluorescence immunoassay (FIA) by commercial kit (Boditech Med Inc. 43 Republic of Korea) by ichroma reader. The levels of 25-OH vitamin D were measured using Euroimmun 25-OH vitamin D ELISA kit based on competitive principle. Glucose oxidase-peroxidase method was used to determined blood glucose using mindray BS 200 chemistry autoanalyzer. HbA1C was determined by using a fluorescence immunoassay (FIA) by commercial kit (Boditech Med Inc. 43 Republic of Korea) by using ichroma reader. Serum C-peptide levels were measured by fluorometric enzyme immunoassay (Tosho. India) with detection range of 0.1 - 1000 ng/ml.

Quality Control

Samples representing normal and pathological level of 25(OH) vitamin D, blood glucose, microalbumin, HbA1C and C-peptide were used for assessment of accuracy and precision of all methods used in analysis, and result ± 2SD of the target values of the control sample were accepted.

Statistical Analysis

SPSS software (version 20) was used for analysis of data. Descriptive statistics was used to analyze the demographic characteristics of the studied groups. t-test was used for comparison of measured variable and the difference was statistically significant at $p \leq 0.05$. Correlation (r) was considered significant at $p \leq 0.05$.

RESULTS

The study population comprised of 120 subjects, 40 patients with diabetic nephropathy complication as test group, with age (53.2 ± 6.7 years) male account 42.5%, while female account 57.5%, 40 control diabetics without nephropathy complication, in addition to 40 healthy control subjects age and gender matched.

Table 1 shows baseline characteristic of study group between patients with nephropathy complication and control group patients without nephropathy complication: There is significant decrease in the mean of serum 25(OH) vitamin D (11.5 ± 3.4 vs. 20.4 ± 3.1, $p \leq 0.00$) and C-peptide (1.14 ± 0.2 vs. 2.23 ± 0.23, p=0.00) in the study group when compared with their control group, with significant increase in HbA1c (10.4 ± 1.6 vs. 8.5 ± 1.2, $p \leq 0.00$) microalbumin (144.5 ± 16.3 vs. 8.5 ± 1.3, $p \leq 0.00$), FBS (206.4 ± 32.9 vs. 182.9 ± 29.1, $p \leq 0.01$) in the study group when compared with their control group ($p \leq 0.05$) in Table 2.

Table 1 Clinical characteristics of the study group

Variables	Healthy subjects	Patients without nephropathy Complication	Patients with nephropathy Complication
Gender (male/female)	(18/22)	(16/24)	(17/23)
Age (year)	50.2 ± 4.3	52.8 ± 6.1	53.2 ± 6.7
Duration of DM (year)	0 ± 0.0	10.6 ± 4.18	13.6 ± 4.695
Body mass index (kg/m^2)	25.9 ± 3.31	27.1 ± 2.8	26.7 ± 4.3
SBP (mmHg)	119.5 ± 6.3	122.8 ± 12.4	117.7 ± 7.8
DBP (mmHg)	77.3 ± 5.4	79.7 ± 7.4	79.3 ± 5.8

Table 2 Comparison of serum 25-OH vitamin D, microalbuminuria, FBG, HbA1c, and C-peptide between the two diabetic groups (N=40)

Variables	Patients without nephropathy Complication	Patients with nephropathy Complication	p-value
FBG mg/dl	182.9 ± 29.13	206.4 ± 32.9	0.01
HbA1c %	8.5 ± 1.2	10.4 ±1.6	0.00
25-OH vit D ng/ml	20.4 ± 3.1	11.5±3.4	0.00
Microalbumin mg/L	8.5 ± 1.2	144.8 ± 16.3	0.00
C-peptide	2.23 ± 0.64	1.14 ± 0.2	0.00
*The mean difference is significant at the $p \leq 0.05$; ** The mean difference is significant at the $p \leq 0.01$; *** The mean difference is significant at the $p \leq 0.001$			

According to serum 25(OH) vitamin D levels (insufficiency and deficiency) in Table 3, Patients with 25-OHD levels below 20 ng/ml had a mean FBG, HbA1c, and microalbumin higher than those with 25-OHD levels ≥ 20 ng/ml (208.4 ± 28.8 mg/dl versus 188.3 ± 21.9 mg/dl, p=0.02; 10.5 ± 1.7% vs. 9.5 ± 1.4%, p=0.05; 191.7± 14.3 mg/l 139.2 ± 16.9 mg/l, p=0.04 respectively) in the study group.

Table 3 Characteristics of the measured variable levels according to 25(OH) vitamin D levels in diabetic patients with nephropathy (N=40)

Variables	Sufficiency 30<70 ng/ml	Insufficiency 20 <30ng/ml (N = 18)	deficiency <20 ng/ml (N=22)	P
FBG mg/dl	--	188.3 ± 21.9	208.4 ± 28.8	0.02
Microalbuminuria Mg/l	---	139.4 ± 16.9	191.7± 14.3	0.04
HbA1c %	---	9.5 ± 1.4	10.5 ± 1.7	0.05
C-peptide ng/ml	----	1.24 ± 0.3	1.12 ± 0.13	-

As illustrated in Table 4, there is significant negative correlation between serum 25-OH vitamin D level with disease duration, (r=0.333, p=0.00) and FBG (r= -0.43, p=0.01 with insignificant correlation with age, (r=0.025, p=0.405) and c-peptide (r= -0.12, p=0.54) in the study group.

Table 4 Correlation between measured variables in diabetic patients with nephropathy complication (N=40)

Variables	Statistic	Age	BMI	SBP	DBP	Duration	FBG	C-peptide
25(OH) Vitamin D Correlation	Pearson correlation	0.16	0.24	0.17	-0.12	0.58*	-0.43*	-0.12
	sign (two tail)	0.41	0.19	0.36	0.54	0.001	0.01	0.54
Microalbuminuria	Pearson correlation	-0.17	-0.31	0.19	0.05	0.18	-0.41*	-0.625*
	Sign (two tail)	0.38	0.09	0.32	0.81	0.36	0.02	0
HbA1c	Pearson correlation	-0.38	0.09	-0.11	0.395*	0.08	-0.2	-0.26
	Sign (two tail)	0.03	-0.07	0.57	0.03	0.69	0.29	0.17
*Correlation is significant at p ≤ 0.05								

As shown in Figures 1 and 2, serum 25(OH) vitamin D level is inversely correlated with HbA1c (r= -0.37, p=0.03), and microalbumin (r= -0.29, p=0.05) in diabetic patient with nephropathy complication.

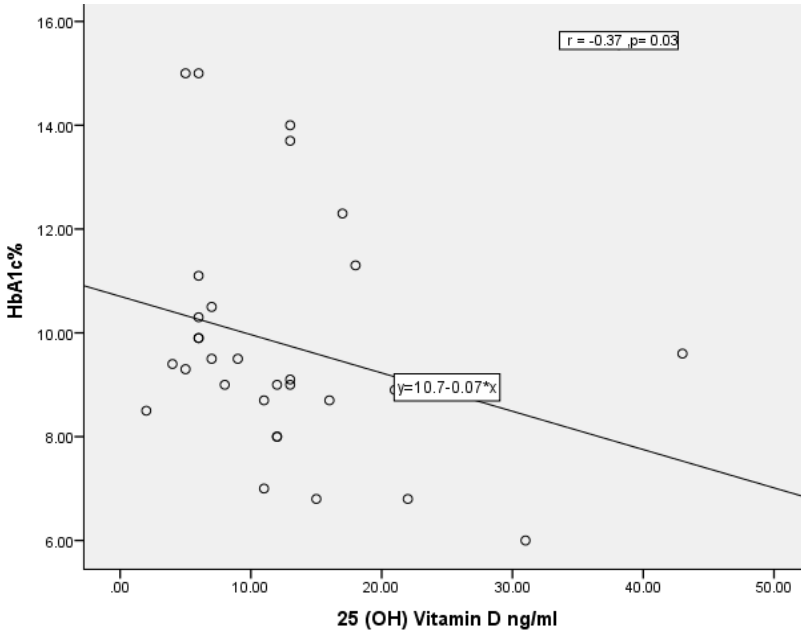

Figure 1 Scatter plot shows the correlation between serum 25(OH) vitamin D level with HbA1c in the study group

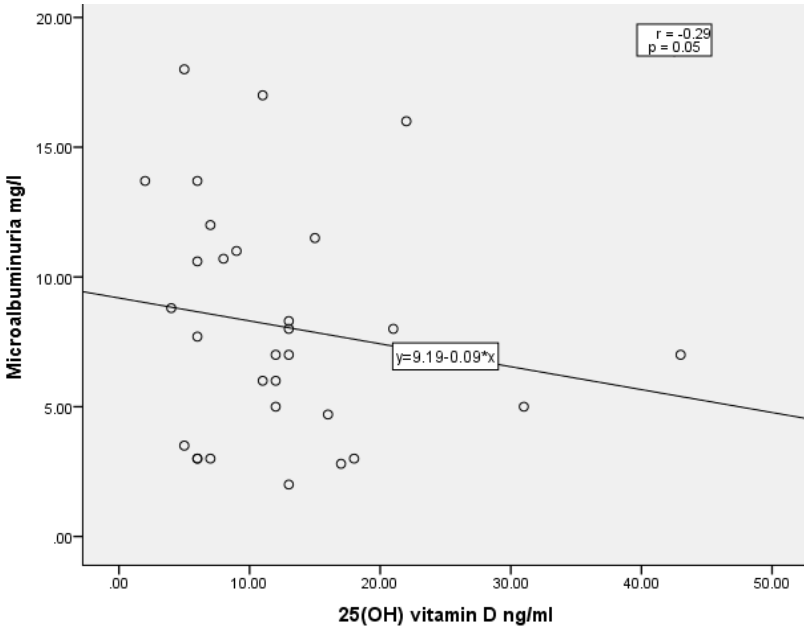

Figure 2 Scatter plot shows the correlation between serum 25(OH) vitamin D level with microalbuminuria in the study group

DISCUSSION

Vitamin D is an important hormone for calcium and phosphorus homeostasis and bone. Recent evidence suggested role of vitamin D in extraskeletal including cancer, autoimmune, infectious glycemic control, and diabetic nephropathy complication [18-22].

In the present study, there was statistical difference in the mean of the 25-hydroxy vitamin D in the study group. The level of 25-hydroxy vitamin D is significantly decreased in patients with nephropathy complication when compared with patients without nephropathy complication. This result agrees with the result obtained by Fiscella, et al. who found that 25-hydroxy vitamin D level in diabetic patient was lower in diabetic patients with microvascular complication compared to without microvascular complication [22]. Pittas, et al. performed a systematic review and meta-analysis on the role of vitamin D and calcium in type 2 diabetes, and observed deficiency of vitamin D in diabetic patients, and supplementation of vitamin D and calcium could delay or prevent the diabetic complications [18].

In the current study, microalbumin is high in test group compared to control group and 25-hydroxy vitamin D is inversely correlated with microalbumin level in patients with nephropathy complication. Vitamin D deficiency increases albuminuria in diabetic patients [23]. In a study conducted by Sánchez, et al., [24] in China, deduced that vitamin D treatment reduced microalbuminuria in patients with type 2 diabetes and nephropathy [23]. Renin-angiotensin-aldosterone system is known to play a major role in diabetic nephropathy. Several therapeutic interventions for diabetic renal disease have been improved over the past few decades [25]. Numerous research studies have illustrated increased activity in the renin-angiotensin-aldosterone system in diabetic patients with nephropathy [26,27]. Vitamin D exerts strong effects on renin-angiotensin-aldosterone system by suppressing the renin release, which is principle stimulator of this system [25-27]. Vitamin D replacement also has beneficial effects on other diabetic nephropathy risk factors, such as hypertension and hyperlipidemia [23,28] Vitamin D deficiency is highly prevalent in patients with advanced CKD. In another study Agarwal, et al. [29] showed that vitamin D replacement therapy reduces levels of albuminuria in patients with chronic renal disease [29]. Serum vitamin D levels in diabetic patients seemed to be linked to nephropathy complication which is confirmed in our study by decreased level of 25(OH) in diabetic patients with nephropathy complication [22].

Our data demonstrated that there is a significant negative correlation between vitamin D level and both FBG and HbA1c in the study group. This result is consistent with the results observed by Sur, et al. [30] whom found that vitamin D levels were decreased and showed a significant negative correlation with glycemic control in cases as

compared to controls, and vitamin D supplementation can lead to good glycemic control [30] Khalid Iqbal, et al. conducted a cross-sectional survey to study the relationship between serum levels of 25-hydroxy vitamin D and glycated hemoglobin (HbA1C) in type-2 diabetic patients, and deduced that the association between vitamin D deficiency and abnormal HbA1C in Pakistani diabetic patients is suggestive that patients with hypovitaminosis D could benefit from vitamin D supplementation [31]. Vitamin D has immunomodulatory action through decreasing cytokine production and lymphocyte proliferation; hence, it reduces the damage of β-cells in the pancreas [32,33].

CONCLUSION

This study illustrated an inverse correlation between 25(OH) vitamin D level and both glycemic control and severity of diabetic nephropathy among Sudanese patients with type 2 diabetes mellitus. Based on several previous researches pointing possible anti-inflammatory and antiangiogenic characters of vitamin D, the role of vitamin D in the progression of diabetic nephropathy and glycemic control warrants further prospective, randomized, controlled trials.

DECLARATIONS

Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

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