Glycemic State of Type 2 Diabetic Chronic Kidney Disease Patients after Vitamin D Replacement Therapy

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycaemia as a result of insulin deficiency, insulin resistance or both.

Objective: To assess the impact of vitamin D replacement therapy on glycemic state in type 2 diabetic chronic kidney disease (CKD) patients.

Patients and Methods: 70 patients previously diagnosed as type 2 DM (according to guidelines used by National Institute of Health USA) attending Al-Azhar Assuit University Hospital, internal medicine department and outpatient clinics was included in our study where vit. D was replaced in our groups and its impact on glycemic state was analyzed by bivariate and multivariate analyses.

Results: Our study is a prospective study revealed a significant negative correlation between 25(OH)D levels and HbA1c values before and after vit. D replacement therapy.

Conclusion: Vitamin D replacement therapy had a beneficial effect on glucose hemostasis via a significant reduction in HbA1c, this emphasizes the potential therapeutic implications of vitamin D supplementation as a promising preventative and therapeutic agent for improved glycemic control among type 2 DM patients with CKD.

Keywords: HbA1c, Type 2 DM, Chronic Kidney Disease, Vit. D replacement, Intervention study.

INTRODUCTION

Diabetes mellitus (DM) is a disordercharacterized by chronic hyperglycaemia as a result of insulin deficiency, insulin resistance or both. Diabetes has a high prevalence with the total number of people with diabetes expected to rise from 366 million in 2011 to 552 million in 2030 [(1)].

Vitamin D has emerged as a potential modifier risk for diabetes. Vitamin D is thought to affect various mechanisms related to the pathophysiology of both types of diabetes, including pancreatic beta-cell dysfunction, impaired insulin action and systemic inflammation; either directly via activation of the vitamin D receptor, or indirectly via regulation of calcium homeostasis [(2)].

Vitamin D deficiency impairs insulin secretion from pancreatic beta-cells [(3)] it also increases insulin resistance [(4)], hence contributing significantly to the pathogenesis of the two types of diabetes and may therefore predispose to the two types of diabetes[(5)].

The effect of vitamin D on pancreatic beta-cells and subsequently on insulin release is mediated via vitamin D receptor (VDR). Vitamin D may affect insulin synthesis and secretion by acting directly via binding of its active form to the VDR expressed in pancreatic β-cells Vitamin D is thought to promote insulin secretion through increasing the cytosolic calcium concentration in beta-cells. This is supported by the presence of the vitamin D response element (VDRE) in the human insulin gene promoter and transcriptional activation of the human insulin gene caused by the active form of vitamin D [(6)]. So, we performed our study to assess the glycemic state of type 2 diabetic chronic kidney disease patients after vitamin D replacement therapy.

AIM OF THE WORK

To assess the impact of vitamin D replacement therapy on glycemic state in type 2 diabetic chronic kidney disease patients.

PATIENTS AND METHODS

This was a prospective study conducted on 70 patients previously diagnosed as type 2 DM (according to guidelines used by National Institute of Health USA) attending Al-Azhar Assuit University Hospital, internal medicine department and outpatient clinics in the period from October 2018 to March 2019.

Our study patients were classified into three groups according to the US Institute of Medicine recommendations for vitamin D.

1. Deficient group: included patients with serum 25(OH)D3 less than 20ng/ml.
2. Insufficient group: included patients with serum 25(OH)D3 of 20-29.9 ng/ml.
3. Sufficient group: included patients with serum 25(OH)D3 $\geq$30 ng/ml.

   All patients were matched with sex, age and residence.

All patients were subjected to the following:

- Full history taking, including age, sex, and detailed drug history.
- Clinical examination, with emphasis on blood pressure, waist circumference, body mass index (BMI).
- Abdominal ultrasonography, for detection of kidney abnormalities and electrocardiography to detect and exclude any cardiac abnormalities.
- Routine laboratory investigations including: CBC, Liver and Kidney functions, fasting and 2hr.

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Postpranial Blood Glucose and Serum Uric Acid.

- Special investigations include assay of serum 25(OH)D3, HbA1c, estimated glomerular filtration rate (eGFR), Albumin/Creatinine Ratio. Calcium, Phosphate, T4, TSH and PTH Levels were estimated.
- Pretreatment and post treatment (with 75000 IU IM injection of Vit.D3 weekly prescribed for 3 months) laboratory parameters will be compared in these patients.

Ethical consideration and Written informed consent:

An approval of the study was obtained from Al- Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

The following were excluded from our study:-

- The non-cooperatives during the study.
- Pregnant women.
- Patients with hyperclacemia or hyperphosphatemia.
- Patients with hematological or solid tumors.
- Patients receiving calcium or vit. D during the last 2 months.
- Patients with thyroid or parathyroid disorders.

At the end of the study the all data were collected, tabulated &statistically analyzed.

- Analysis of data was carried out by an IBM computer using statistical program for social science (SPSS) (software and services, North California, USA) version 18 as follows:

1. Description of quantitative variables as mean, SD, and range.
2. Description of qualitative variables as number and percentage.
3. An unpaired *t*-test was used to compare two groups in terms of quantitative variable.
4. *P* value >0.05 non-significant, *P* value ≤0.05 significant and *P* value <0.01 highly significant).
5. Relationships between parameters were analyzed using the Pearson correlation coefficients (*r*).

RESULTS

Table (1): Description of demographic data in studied patients.

Variables		Studied patients (N = 70)
Age (years)	Mean	64.2
	±SD	10.5
	Min	51
	Max	73
	Range	22 (51 – 73)
Sex	Male	45 (64.3%)
	Female	25 (35.7%)
Residence	Rural	60 (85.7%)
	Urban	10 (14.3%)

This table shows description of demographic data in studied patients. The mean age of studied patients was 64.2 ± 10.5 years. As regard sex, 45 patients (64.3 %) were males and 25 patients (35.7%) were females. As regard residence, 60 patients (85.7 %) were from rural and 10 patients (14.3%) were from urban.

Table (2): Classification of the studied cases according to US Institute of Medicine (IOM) classification for vitamin D.

Vitamin D status	N	%
Sufficiency {(25(OH)D > 30 ng/dl}	**20**	**28.6%**
Insufficiency{(25(OH)D 20-29.9 ng/dl}	**16**	**22.9%**
Deficiency{(25(OH)D < 20 ng/dl}	**34**	**48.5%**

20 patients (28.6%) were sufficient, 16 patients (22.9%) were insufficient and 34 patients (48.5%) were deficient. As regard vitamin D status. Table (2).

Table (3): Comparison between eGFR, HA1C and 25 (OH)D between studied patients (Before therapy).

parameters :	Sufficiency N=20	Insufficiency N=16	Deficiency N=34	P-Value
eGFR, (mL/min per1.73m2)	39.2 ± 2.3	41.4 ± 3.2	48.7 ± 1.7	**< 0.001***
HA1c, (%)	6.4 ± 1.3	7.2 ± 1.4	9.4 ± 2.1	**< 0.001***
25(OH)D, (ng/mL)	44.8 ± 3.6	25.2 ± 2.6	11.2 ± 2.5	**< 0.001***

** P-value < 0.001 is considered highly significant.*

There is a highly statistical difference (p-value <0.001) between vitamin D sufficient, insufficient and deficient patients as regard eGFR, HA1C and 25(OH)D. Table (3).

Table (4): Comparison between eGFR, HA1C and 25(OH)D before and after vitamin D therapy in vitamin D sufficient group.

Sufficient patients / Variables	Before treatment N=20	After treatment N=20	P-Value
eGFR, (mL/min per1.73m2)	39.2 ± 2.3	40.5 ± 1.4	**0.037***
HA1c, (%)	6.4 ± 1.3	5.9 ± 1.1	**0.2**
25(OH)D, (ng/mL)	44.8 ± 3.6	66.8 ± 1.7	**< 0.001***

** p-value < 0.001 is considered highly significant.*
*** p-value < 0.05 is considered significant.*
Sufficient group shows highly significant improvement in serum 25(OH)D after vit.D replacement therapy (p-value < 0.001), significant improvement in eGFR (p-value <0.05). Table (4).

Table (5): Comparison between eGFR, HA1C and 25 (OH)D before and after vitamin D therapy in vitamin D insufficient group.

Insufficient patients / Variables	Before treatment N=16	After treatment N=16	P-Value
eGFR, (mL/min per1.73m2)	41.4 ± 3.2	42.5 ± 4.4	**0.42**
HA1c, (%)	7.2 ± 1.4	6.2 ± 1.1	**0.03****
25(OH)D, (ng/mL)	25.2 ± 2.6	59.7 ± 11.7	**< 0.001***

** p-value < 0.001 is considered highly significant.*
*** p-value < 0.05 is considered significant.*
Insufficient group shows highly significant improvement in serum Vit.D after replacement therapy p-value <0.001), in addition to significant improvement in eGFR after vit.D replacement therapy (p-value <0.05) without considered improvement in HbA1c. Table (5).

Table (6): Comparison between eGFR, HA1C and 25 (OH)D before and after vitamin D therapy in vitamin D deficient group.

Deficient patients / Variables	Before treatment N=34	After treatment N=34	P-Value
eGFR, (mL/min per1.73m2)	48.7 ± 1.7	49.3 ± 3.4	0.36
HA1c, (%)	9.4 ± 2.1	7.4 ± 1.3	**< 0.001***
25(OH)D, (ng/mL)	11.2 ± 2.5	39.9 ± 5.9	**< 0.001***

** p-value < 0.001 is considered highly significant.*
On the other hand, deficient group shows, highly significant improvement in serum 25(OH)D and HbA1c after vit.D improvement. Table (6).

DISCUSSION

We performed this prospective study on 70 patients previously diagnosed as type 2 diabetic chronic kidney disease (according to guidelines used by National Institute of Health USA) attending Al-Azhar Assuit University Hospital, internal medicine department and outpatient clinics. In this study we classified our patients into three groups according to the US Institute of Medicine recommendations for vitamin D. In the present study the mean age of patients was 64.2 ± 10.5 years. As regard sex, 45 patients (64.3 %) were males and 25 patients (35.7%) were females. As regard residence, 60 patients (85.7 %) were from rural and 10 patients (14.3%) were from urban.

On the other hand, there was statistically significant (p-value = 0.01) negative correlation (r = -0.9) between vitamin. D and serum creatinine in the studied patients. No statistical significant (p-value >0.05) correlation between vitamin D and other

studied parameters in studied patients.

Before starting vitamin D replacement therapy there is highly statistical difference (p-value <0.001) between vitamin D sufficient, insufficient and deficient patients as regard eGFR, HbA1C and serum 25(OH)D, where the mean HbA1c values were 9.4 ± 2.1% in the group with vitamin deficiency, 7.2 ± 1.4% in the insufficiency group, and 6.4±1.3% in the sufficiency group (<0.001). These result similar to the previously published data by **Haitham *et al.*** [7] which was done on 90 subjects (70 patients and 20 as healthy control) carried out at Internal medicine department, Al- Azhar Assuit University, were matching with age , sex and residence.

About 40% of participants were with good glycemic control, 30% of participants were with moderate glycemic control and 30% of participants were with poor glycemic control. Half of cases were Vitamin D deficient, 30% of them are insufficient, and 20% are sufficient. Also results showed that level of serum 25(OH) Vitamin D correlate inversely with level of HbA1C irrespective of eGFR or age of patients. The study reported a significant inverse relationship between serum 25(OH) D and HbA1c levels in type 2 diabetics with suboptimal glycemic control and different stages of CKD (P <0.05) .Our result similar to the previously published data by **Kajbaf *et al.*** [8]**,** which was done in 245 patients meeting the selection criteria (mean ± SD age: 65±11; male/female gender 342/200, 63%/37%).

The mean HbA1c values were 8.4±2.0% in the subgroup with vitamin deficiency, 7.3±1.5% in the insufficiency group, and 6.7±1.0% in the sufficiency group (p-value <0.0001), which found statistical difference between serum 25(OH) D and HbA1c levels for the study population as a whole and in the CKD subgroups (p-value <0.0001).

Also our study is agree with a cross-sectional study were carried out between September 2015 and July 2016 at the University of Malaysia Medical Center, by **Lee and Chen** [9] which was done on 100 participants with the mean (±SD) age were 60.5±9.0 years, whereas mean HbA1c were 7.9±1.6% and serum 25(OH)D were 37.1±22.2 nmol/L. HbA1c was negatively correlated with serum 25(OH) D (r= -0.314, p-value 0.002).

Our findings showed that, high prevalence of hypovitaminosis D (approx. 71.4%) with higher levels of HbA1c, which agree with the previously published data by **Yilmaz *et al.*** [10] demonstrating that, 73.0% prevalence of hypovitaminosis D (higher in females) among Turkish Type 2 DM patients that was done on a total of 1,463 patients with Type 2 DM and CKD (aged 14–88 years), 927 females and 536 males, were included in there study.

Conversely a cross sectional Canadian study conducted on 60 patients , most of them were Type 2 DM (90%) and all of them were CKD; the study showed no significant correlation was observed between level of HbA1c and 25(OH) vitamin D in those patients, which may attributed to small sample size, **Hoffmann *et al.*** [11].

In our study there is highly statistical significant positive value (p-value <0.001) of serum 25(OH)D as its level increased after therapy comparing its level before Vitamin D replacement therapy. In vitamin D sufficient group, (before vitamin D therapy serum 25 (OH)D was 44.8 ± 13.6 ng/mL comparing its level after therapy 66.8±10.7ng/mL) and insufficient group (before vitamin D therapy serum 25 (OH)D was 25.2 ± 2.6 ng/mL comparing its level after therapy 59.7±11.7 ng/mL) and deficient group (before vitamin D therapy serum 25 (OH)D was11.2±4.5 ng/mL comparing its level after therapy 39.9±15.9 ng/mL).

Also our study shows a statistically significant value of HbA1C as its value reduced after vitamin D replacement therapy (p-value <0.05).

In vitamin D sufficient group (HbA1c was 6.4±1.3% before therapy versus after therapy was 5.9±1.1%) and insufficient groups (HbA1c was 7.2±1.4% before therapy versus after therapy was 6.2±1.1%) and with (p-value < 0.001) in vitamin D deficient group (HbA1c was 9.4±2.1% before therapy versus after therapy was 7.4±1.3%).

Our study agree with other study that was Prospective, open label, comparative, randomized, parallel group, two arm interventional study, which was done by **Deepak and Mohd** [12] conducted on 120 Indian patients total 120 patients were classified in two groups: 60 as control and 60 as cases, with Type 2 DM, with HbA1c level >7.0% and <8.5%, whom supplied by vitamin D supplement, Single sachet dose, equivalent to l gm containing 60,000 IU of Cholecalciferol. To be supplemented once a week for 2 months followed by once a month for 4 months, additionally: 2000 IU of Cholecalciferol Capsule to be supplemented once daily. Comparison of two active treatment groups over a period of six months.

The effect of Vitamin D supplement was observed on various parameters i.e. FBG, PPBS, HbA1c. In Group T (cases), HbA1c 7.76 to 6.70 (r-1.06), but in Group C (control), HbA1c 7.80 to 7.22 (-0.58). Group T statistically highly significant than Group C in improving glycemic indices. In control Group C there was minimal reduction in mean HbA1c as it decreased from 7.8 ± 0.47 to 7.4 ± 0.51 in 3 months and then to 7.2 ± 0.59 at 6 months reflecting a total reduction of 7.43%. In contrast during the same period in Treatment Group T, the Mean HbA1c showed a decrease from 7.8 ± 0.51 to 7.2 ± 0.51 at 3 months and further to 6.7 ± 0.39 after 6 months which approved that in treatment group Vitamin D supplement was responsible for improved levels of HbA1c.

Our study conversely with the study

performed by **Clavo and Romero** [13] where they studied on type 2 diabetic patients with vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) lower than 20ng/ml). They were treated with 16,000IU of calcifediol orally once a week for a minimum of 8 weeks. Twenty eight patients were treated for a mean time of 84.1 days (range 56 to 120 days). All patients achieved serum levels of serum 25(OH)D higher than 20ng/ml. There was a significant reduction in fasting glucose (145.6±35.5 vs. 131.7±30.4mg/dl, $p<0.001$).

This lower level of serum 25(OH)D among diabetic patients and higher $HbA1_c$ in cases of hypovitaminosis D than with vitamin D sufficiency was also reported by **Kajbaf *et al.*** [14] in other studies on diabetic patients with various stages of CKD**.**

The significant improvement in $HbA1_c$ levels after vitamin D replacement therapy that we observed emphasizes the association of vitamin D levels with glucose hemostasis in Type 2 DM, and the potential therapeutic implications of this association in achieving improved glycemic control in Type 2 DM management which agree with **Kostoglou *et al.*** [15].

Similar to our findings, the likely benefit of vitamin D substitution for a better Type 2 DM prognosis was suggested in a 15-year longitudinal study among Type 2 DM patients by **Joergensen *et al.*** [16]**.** Clinical trials, however, by **Shehab *et al.*** [17] have revealed inconsistent findings on the impact of maintaining adequate vitamin D status and/or high-dose vitamin replacement on long-term glycemic control in Type 2 DM patients**.**

Thus, the need for validation by further large-scale, cross-sectional, and interventional clinical studies is emphasized.

CONCLUSION

Vitamin D replacement therapy had a beneficial effect on glucose hemostasis via a significant reduction in HbA1c, this emphasizes the potential therapeutic implications of vitamin D supplementation as a promising preventative and therapeutic agent for improved glycemic control among type 2 DM patients with CKD.

Certain ***limitations*** to this study included that it is a single-center design and thus an inability to generalize our findings to the overall diabetic population due to small number of participates, effect of anti-diabetic drugs not addressed and also the fact that there was no standard duration of vitamin D treatment.

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