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Retrospective Cohort Study

Vitamin D levels in subjects with or without chronic kidney disease among Veterans with diabetes in North East United States

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Abstract**AIM**

To evaluate the prevalence of vitamin D deficiency and its relation to diabetes and kidney disease in Veterans residing in the North East United States (VISN 2).

METHODS

In this retrospective study, we used data from the computerized patient record system at Stratton Veterans Administration Medical Center at Albany, NY (VHA) for those patients who had 25-hydroxyvitamin D levels and 1,25 (OH) vitamin D levels measured between 2007 and 2010. We collected demographic information including age, sex, body mass index and race; clinical data including diabetes, hypertension and CAD; and laboratory data including calcium, creatinine and parathyroid hormone (PTH) (intact). Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L), and insufficiency is defined as a serum 25-hydroxyvitamin D level of 20 to 30 ng/mL (50 to 75 nmol/L).

RESULTS

Data was available for approximately 68000 subjects. We identified 64144 subjects for analysis after exclusion of duplicates. Among them, 27098 had diabetes. The

mean age of subjects with diabetes was 68 ± 11 with a mean body mass index (BMI) of 32 ± 7 and duration of diabetes of 5.6 ± 3.2 years. The mean 25 (OH) vitamin D level among subjects with diabetes was 27 ± 11.6 . There was no significant difference in 25 (OH) vitamin D levels between subjects with diabetes and glomerular filtration rate (e-GFR) < 60 compared to those with e-GFR ≥ 60 . As expected, subjects with e-GFR < 60 had significantly lower 1,25 (OH) vitamin D levels and significantly elevated PTH-intact. Of the 64144 subjects, 580 had end-stage renal disease. Of those, 407 had diabetes and 173 did not. Vitamin D levels in both groups were in the insufficiency range and there was no significant difference irrespective of presence or absence of diabetes. Subjects with vitamin D levels less than 20 ng/mL had a higher BMI and elevated PTH, and higher HbA1C levels compared to those with vitamin D levels more than 20 ng/mL.

CONCLUSION

We conclude that we need to keep a close eye on vitamin D levels in subjects with mild chronic kidney disease as well as those with moderate control of diabetes.

Key words: Vitamin D; Type 2 diabetes; Men; Chronic kidney disease; End stage renal disease

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Core tip: This retrospective study evaluated the prevalence of vitamin D deficiency among Veterans in the North East United States, for those patients who had vitamin D levels measured between 2007 and 2010. The data collected include the data of 27098 subjects with diabetes with mean age of 68 and mean duration of diabetes of 5.6 years. There was no significant difference in 25 (OH) vitamin D levels between subjects with $>$ glomerular filtration rate (e-GFR) < 60 and eGFR ≥ 60 but with decreased levels of 1,25 (OH) vitamin D and elevated parathyroid hormone. Vitamin D levels did not differ between subjects with or without diabetes.

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INTRODUCTION

The prevalence and incidence of type 2 diabetes mellitus (T2DM) is increasing. As per the National Diabetes Statistics Report, 2014, 29.1 million people or 9.3% of the population have diabetes. Vitamin D plays an important role in calcium homeostasis and maintenance of optimal skeletal health. The vitamin D status is marked by the serum levels of 25-hydroxyvitamin D concentration^[1]. Factors that influence circulating vitamin D levels include race, season, body mass index, and age^[1]. Sources of vitamin D in humans include

exposure to sunlight, diet, and dietary supplements. In the presence of vitamin D, calcium is actively absorbed from the small intestine. Vitamin D refers to vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol). Vitamin D deficiency can lead to rickets in children, osteomalacia in adults, myopathy and a variety of extra skeletal problems, including cardiovascular disease, infection, malignancy, and death^[1-3]. Vitamin D from the dietary resources and sun exposure gets metabolized in the liver to 25-hydroxyvitamin D^[1]. Vitamin D insufficiency affects almost 50% of the population worldwide^[1,4]. McMurtry *et al*^[5] reported that most Veterans living in nursing homes have vitamin D insufficiency. Later, the prevalence of vitamin D deficiency/insufficiency in long-term care patients at a Veterans Health Administration (VHA) hospital was reported to be as high. McMurtry *et al*^[6] stated that 49% of them had sufficient vitamin D, 14% had insufficiency, and 37% had deficiency. The aim of this study was to evaluate the prevalence of vitamin D deficiency among Veterans with diabetes in North East United States. In addition we planned to compare vitamin D levels in subjects with diabetes with or without chronic kidney disease (CKD) and end stage renal disease (ESRD).

MATERIALS AND METHODS

Design

Single center, retrospective database study.

Study site

Stratton Veterans Administration Medical Center, Albany, NY, United States.

Information collected

Using the data base of the Veterans Health Administration (VHA) computerized patient record system (CPRS) at Stratton Veterans Administration Medical Center, we collected the data for those patients who had 25-hydroxyvitamin D levels and 1,25 dihydroxy vitamin D levels measured between 2007 and 2010, after the approval of the protocol both by the Institutional Review Board (IRB) and Research and Development (R and D) Committees at the VA Medical Center. We collected demographic information including age, sex, body mass index and race; clinical data including diabetes, hypertension and CAD; and laboratory data including calcium, creatinine and parathyroid hormone (PTH) (intact). The vitamin D levels were measured by immunoassay.

Definitions

Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L), and insufficiency is defined as a serum 25-hydroxyvitamin D level of 20-30 ng/mL (50 to 75 nmol/L).

Statistical analysis

The statistical analysis performed include: Data is

Table 1 Clinical and biochemical parameters in all subjects with diabetes (n = 27098)

Parameter	Mean ± SD
Age	68 ± 11
BMI	32 ± 7
DM duration (yr)	5.6 ± 3.2
HTN (%)	94
Vit D	27 ± 11.6
Cre	1.38 ± 0.9
eGFR	66 ± 24
Calcium	9.5 ± 0.5
Glucose	142 ± 64
HbA1C	7.2 ± 1.4
PTH	126 ± 121
1,25 Vit D	28 ± 16
IHD (%)	24

BMI: Body mass index; Dur of DM: Duration of diabetes; HTN: Hypertension; Vit D: Vitamin D; Cre: Creatinine; PTH: Parathyroid hormone; IHD: Ischemic heart disease.

expressed as mean ± SD. Comparison of clinical and lab parameters of subjects with GFR < 60 and ≥ 60 with diabetes is carried out. Comparison of clinical and lab parameters of subjects with vitamin D levels < 20 and > 20 with diabetes is carried out. Comparison of clinical and lab parameters of subjects with ESRD with or without diabetes was carried out.

RESULTS

Data was available for approximately 68000 subjects. We identified 64144 subjects for analysis after exclusion of duplicates. Among them, 27098 had diabetes. The mean age of subjects with diabetes was 68 ± 11 with a mean body mass index (BMI) of 32 ± 7 and duration of diabetes of 5.6 ± 3.2 years. The mean 25 (OH) vitamin D level among subjects with diabetes was 27 ± 11.6. The clinical and biochemical parameters of all the subjects with diabetes are shown in Table 1. The prevalence of vitamin D deficiency is 31% and insufficiency is 35%. We noted negative correlation of 25 (OH) vitamin D levels with BMI ($r = -0.12$; $P < 0.001$), HbA1C ($r = -0.14$; $P < 0.001$), glucose ($r = -0.12$; $P < 0.001$), and PTH levels ($r = -0.11$; $P < 0.0001$). We noted that the 25 (OH) vitamin D levels did not correlate with age or duration of diabetes or creatinine. In subjects with decreased GFR, the vitamin D levels correlated with age. Comparison of the clinical and biochemical parameters of the subjects with eGFR < 60 and eGFR ≥ 60 are shown in Table 2.

Subjects with hypovitaminosis D in comparison with patients with vitamin D sufficiency, had higher BMI (33 ± 7.0 vs 32 ± 6.0; $P = 2.53E-08$); higher HbA1C (7.4 ± 1.6 vs 7.0 ± 1.3; $P = 2.5E-139$); higher PTH values (142 ± 1074 vs 117 ± 119.0; $P = 2.86E-89$) as in Table 3. There were 580 subjects with ESRD. Among these subjects with ESRD, 407 had diabetes and 173 without diabetes. The comparative clinical and biochemical data of the subjects with ESRD are shown in Table 4 showing the differences between subjects with and without diabetes.

Table 2 Clinical and laboratory parameters in subjects with diabetes with glomerular filtration rate < 60 compared to those with glomerular filtration rate ≥ 60

	Mean ± SD eGFR ≥ 60	Mean ± SD eGFR < 60	P value
Age	64.9 ± 11	72.5 ± 10	0
BMI	32 ± 7	31.5 ± 6.5	1.09E-16
Dur of DM	5.2 ± 3.2	6.33 ± 3	1.90E-165
HTN	92%	97%	2.10E-99
Vit D	27 ± 11.5	26.6 ± 12	0.751554
Cre	1.0 ± 0.16	2.02 ± 1.3	0
eGFR	81 ± 16	41.6 ± 13	0
Calcium	9.6 ± 0.46	9.4 ± 0.6	4.23E-97
Glu	141 ± 60	144 ± 68	4.25E-05
HbA1C	7.2 ± 1.46	7.25 ± 1.4	0.018789
PTH	64 ± 43	152 ± 133	1.20E-236
1,25 Vit D	34.8 ± 16	25 ± 14	1.30E-20

GFR: Glomerular filtration rate; BMI: Body mass index; Cre: Creatinine; HTN: Hypertension; Vit D: Vitamin D; PTH: Parathyroid hormone.

In subjects with ESRD the 25 (OH) vitamin D levels correlated significantly with age.

DISCUSSION

There are several relevant features in the current study. The first notable point in our study is the high prevalence of vitamin D deficiency (31%) and insufficiency (35%) among subjects with diabetes. We noted that patients with hypovitaminosis D, compared to the patients with vitamin D sufficiency, had higher BMI, higher HbA1C and higher glucose levels. Our data is similar to the other reports^[7] that correlation of low vitamin D levels with high body fat and glucose levels^[7]. In our data base study, we noted a negative association of vitamin D levels with HbA1C indicating the association with glycemic control. This is similar to other studies. Studies on supplementation of vitamin D and calcium has been shown to improve insulin sensitivity in prediabetes^[8] and beneficial effect on glycemic parameters in male type 2 diabetic patients^[9], whereas no effect was noted on long-term glycemic control for T2DM in a South Korean study^[10]. Studies in adults with prediabetes, who are at risk for type 2 diabetes, short-term supplementation of vitamin D though improved β cell function but had a marginal effect on attenuating the rise in HbA1C^[11].

Comparison of the clinical and biochemical parameters of the subjects with eGFR < 60 and eGFR ≥ 60 are shown in Table 2. Prevalence of vitamin D deficiency is common in chronic kidney disease, but lower intake was considered unlikely to be the cause^[12]. In CKD, altered vitamin D metabolism leads to secondary hyperparathyroidism and CKD-mineral bone disease (CKD-MBD). Studies suggest that in patients with CKD, vitamin D deficiency was reported to be associated with increased cardiovascular related morbidity, mortality and all-cause mortality^[13,14]; in both type 1 and 2 DM^[15,16]. We noted that the 25 (OH) vitamin D levels did not correlate with age or duration of diabetes or creatinine.

Table 3 Clinical and laboratory parameters in subjects with diabetes mellitus with vitamin D levels < 20 and > 20

	Vit D < 20 Mean ± SD	Vit D > 20 Mean ± SD	P-value
Age	66 ± 12	68 ± 11	2.53E-08
BMI	33 ± 7	32 ± 6	5.09E-12
HTN (%)	93	90	NS
25, OH Vit D	14.2 ± 4	32 ± 9	0
Creatinine	1.4 ± 1.0	1.3 ± 0.8	4.60E-130
eGFR	67 ± 26	67 ± 24	7.96E-23
Calcium	9.5 ± 1.4	9.6 ± 1.8	1.20E-208
Glucose	148 ± 69	136 ± 56	1.20E-111
HbA1C	7.4 ± 1.6	7.0 ± 1.3	2.50E-139
PTH	142 ± 174	117 ± 119	2.86E-89

GFR: Glomerular filtration rate; BMI: Body mass index; HTN: Hypertension; Vit D: Vitamin D; PTH: Parathyroid hormone.

Among 580 subjects with end stage renal disease (ESRD), 407 had diabetes and 173 did not. The prevalence of patients on renal replacement therapy for ESRD is increasing globally, diabetes being the leading cause; with an increase in prevalence of ESRD attributed to diabetic kidney disease increased by 2.5 fold in the last decade^[17,18]. The relatively increased number of subjects receiving renal replacement therapy among subjects with diabetes is similar to the renal databases from United States and United Kingdom^[17,18]. Vitamin D deficiency was common among subjects with ESRD on dialysis with no significant difference between subjects with or without diabetes. This is in contrast to the other published data^[19]. Schiller and associates reported that vitamin D deficiency is significantly higher prevalence in patients on hemodialysis secondary to diabetic kidney disease and have a higher overall mortality than non-DM patients. They also suggested mandatory screening for vitamin D deficiency as an optimal risk reduction strategy^[19].

The Third National Health and Nutrition Examination Survey (NHANES III), vitamin D levels in the lowest quartile (< 17.8 ng/mL) was reported to be independently associated with increased all-cause mortality^[20]. Regarding the micro and macrovascular complications and association with vitamin D deficiency, the literature has varied data. Subjects with diabetic neuropathy said to have lower vitamin D levels (81.5%) compared to those without neuropathy (60.4%)^[21]. Regarding vitamin D levels in subjects with diabetic retinopathy, some authors report that the prevalence of diabetic retinopathy doubles at vitamin D level of less than 15.57 ng/mL^[22], while others did not find any association between diabetic retinopathy and its severity and vitamin D insufficiency^[23]. In the NHANES data, the prevalence of peripheral arterial disease is high among subjects with low vitamin D^[24]. Some studies suggest improvement in HbA1C with vitamin D supplementation in subjects with T2D^[25], while others did not notice significant improvement in glycemic control^[26].

Limitations of this study: Information on supple-

Table 4 Clinical and laboratory parameters in subjects with end stage renal disease and with or without diabetes mellitus

	Diabetes (407) Mean ± SD	Without diabetes (173) Mean ± SD	P-value
Age	67 ± 2	68 ± 4	0.0824
BMI	30.5 ± 2	25.2 ± 4	3.00E-13
HTN (%)	98	91	
25 (OH Vit D)	24 ± 1.4	24 ± 1.6	0.129
Creatinine	6.6 ± 1.1	7.1 ± 1.1	0.2588
eGFR	10 ± 2	9.1 ± 2.2	0.5871
Calcium	8.9 ± 0.1	8.9 ± 1.1	0.2059
Glucose	147 ± 12	104 ± 8	3.00E-47
HbA1C	6.8 ± 1.4	5.5 ± 0.4	9.29E-16
PTH	353 ± 305	346 ± 290	0.4339

GFR: Glomerular filtration rate; BMI: Body mass index; HTN: Hypertension; Vit D: Vitamin D; PTH: Parathyroid hormone.

mentation of vitamin D or associated other medical problems that possibly might have led to vitamin D deficiency are not included into the data retrieved.

In conclusion, vitamin D deficiency is high among Veterans from the North East. Since vitamin D deficiency among subjects with diabetes is associated with higher BMI and higher HbA1C, it is important to screen the obese diabetics as well as moderate to poor glycemic control subjects as it can be easily supplemented. That may result in improvement in skeletal health in subjects with diabetes who have a higher risk for fractures.

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COMMENTS

Background

Vitamin D deficiency is reported to be common among subjects with diabetes. Similarly vitamin D is a common association in subjects with chronic kidney disease. Several reports in literature indicate vitamin D is common in North East United States.

Research frontiers

Since the data suggests that vitamin D deficiency is more common in subjects with poor control as well as those with higher body mass index (BMI), it is worthwhile look into the causes of poor glycemic control and supplementing vitamin D along with improving glycemic control.

Innovations and breakthroughs

The current data is nothing innovative or breakthrough. The data suggests that vitamin D deficiency is more common in subjects with poor control as well as those with higher BMI.

Applications

It is advisable to monitor vitamin D status in diabetes subjects with poor

glycemic control and or obesity.

Terminology

Vitamin D deficiency: Serum 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L); Vitamin D insufficiency: Serum 25-hydroxyvitamin D level of 20-30 ng/mL (50 to 75 nmol/L). CKD: Chronic kidney disease; ESRD: End stage renal disease.

Peer-review

The aim of this study was to evaluate the prevalence of vitamin D deficiency and its relation to diabetes and kidney disease in Veterans residing in the North East United States.

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