Medicine Science *Metabolic control, albumin excretion rate and 25-hydroxyvitamin D*
2013;2(4):852-62
Original Investigation *doi: 10.5455/medscience.2013.02.8089*

Relationship between 25-Hydroxyvitamin D Level and Metabolic Control and Albumin Excretion Rate in Elderly Patients with Type 2 Diabetes Mellitus

Fulden Sarac[1], Sumru Savas[1], Sefa Sarac[2], Fehmi Akcicek[1]

[1] Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey

[2] Department of Cardiology, Atatürk Training and Research Hospital, Izmir, Turkey

Abstract

The aims of the study were 1. to investigate the frequency of 25-hydroxyvitamin D deficiency and 2. to observe the relationships between D vitamin supplementation and albumin excretion in elderly patients with type 2 diabetes mellitus (DM). The study population included 100 patients with type 2 DM treated with insulin therapy (mean age 56.1±8.8 yrs). Of 100 patients, 30 (mean age 65.4±6.4 yrs) had low 25-hydroxyvitamin (OH) D (25(OH)D) levels. Patients with low 25(OH)D levels received 50.000 unit of vitamin D3 orally every three weeks for 6 months. Albumin excretion rate was measured in patients with low level 25(OH) D before and after D vitamin supplementation. Amongst patients with deficiency; 10 (33.3%) had insufficient vitamin D levels, 19 (63.4%) had deficient levels, 1 (3.3%) had severe deficiency. There were statistically significant differences for plasma levels of A1c (p=0.003), postprandial glucose (p=0.0001), triglyceride (p=0.04), total-Cholesterol (p=0.03), LDL-Cholesterol (p=0.02), and HDL-Cholesterol (p=0.001) in patients with deficiency before and after D vitamin supplementation. There was high frequency of 25(OH)D deficiency in patients with type 2 diabetic patients. And also, D vitamin supplementation changed metabolic parameters such as triglyceride, total-Cholesterol, LDL-Cholesterol and HDL-Cholesterol, postprandial glucose and A1c levels but not albumin excretion rate.

Key Words: 25-hydroxyvitamin D, diabetes mellitus, albumin excretion rate, metabolic control

(Rec.Date: Apr 05, 2013 Accept Date: May 13, 2013)

Corresponding Author*:* Fulden Sarac, Department of Geriatric Medicine, Ege University Medical Faculty, 5th Floor, Bornova, Izmir, Turkey
E-Mail: fuldensarac@yahoo.com **Phone:** +90 232 373 7701

Introduction

There is a tendency in increased prevalence of type-2 diabetes mellitus (DM) in elderly patients along with increased life expectancy [1-4]. Age has become the most dominant factor in the etiology of vitamin D deficiency [3, 4]. In patients with established DM and in the general population, low 25-hydroxyvitamin (OH) D (25(OH)D) levels are associated with higher fasting glucose and higher levels of glycated haemoglobin [5, 6]. There are several mechanisms whereby vitamin D might alter glucose metabolism. Vitamin D is known to have antiinflammatory and immunomodulatory effects [7]. This could ameliorate low-grade chronic inflammation that has been implicated in insulin resistance in type 2 DM [8]. Vitamin D may also stimulate insulin release by pancreatic ß-cells [9, 10]. In a previous study, Yılmaz et al. [11] suggested that 73% of type 2 diabetic patients had vitamin D deficiency. Vitamin D deficiency predicted higher fasting and postprandial blood glucose and also disregulation of diabetes. Also, vitamin D supplementation may have a role in modifying other aspects of the metabolic and cardiovascular derangements that accompany type 2 diabetes [12]. Recently, Joergensen et al. [13] suggested that in high-risk type 2 diabetic patients with elevated urinary albumin excretion rate, low levels of vitamin D were associated with asymptomatic coronary artery disease. However, no many studies related to relationship between D vitamin supplementation and albümin excretion rate in elderly patients with type 2 diabetes mellitus. Therefore, The aims of the study were 1. to investigate the frequency of 25(OH)D deficiency and 2. to observe the relationship between D vitamin supplementation and albumin excretion in elderly patients with type 2 DM.

Subjects and Methods

100 patients with type 2 DM treated with insulin therapy (71 females, 29 males, mean age 56.1±8.8 yrs) were enrolled in the study. Of 100 patients, 30 (17 females, 13 males, mean age 65.4±6.4 yrs) had low 25(OH) D level. Patients with low 25(OH)D level received 50.000 unit of vitamin D3 orally per three weeks for 6 months. Albumin excretion rate (AER) was measured in patients with low level 25(OH) D before and after D vitamin supplementation. All the data were evaluated retrospectively.

Anthropometric measurements were made in all subjects. A two point bioelectrical impedance apparatus calibrated for adults (Tanita TBF 300, TANITA Corp.) was used to measure the percentage body fat (%BF).

Serum concentrations of glucose, triglyceride, total and HDL-Cholesterol were determined by enzymatic procedures. Plasma A1c levels and AER were measured by enzymatic and chromatographic methods using commercial kits (Bio-system S.A and Human Germany) respectively. Serum 25(OH)D was measured by radioimmunoassay (RIA) (RIA kit, DiaSorin, Stillwater, MN). The intra- and interassay coefficients of variation for vitamin D were 8.1% and 10.2%, respectively. Patients were classified as having normoalbuminuria (urinary albümin excretion [(UAE<30 mg/24 h), microalbuminuria, (UAE 30–299 mg/24 h), or macroalbuminuria (UAE≥300 mg/24 h)] at baseline.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows (13.0) software package. Numerical variables were expressed as mean ± standard deviation. The groups were compared using the Mann Whitney test.

Results

The characteristics and clinical findings of the study groups are shown in Table 1. There were statistically significant differences for systolic (p=0.03) and diastolic (p= 0.05) blood pressures between diabetic patients with and without 25(OH)D deficiency. In study group (n= 100), 30 patients had low 25(OH)D levels. 10 of them (33.3%) had insufficient vitamin D levels (20 to <30 nmol/L), 19 (63.4%) had deficient levels (10 to <20 ng/mL), 1 (3.3%) had severe deficiency (<10 nmol/L) in patients with deficiency.

Among 70 diabetic patients without deficiency, 22.0% were smokers and 20.0% informed alcohol consumption. However, 30.0% of diabetic patients with low 25(OH)D levels were smokers and only 16.6% of them consumed alcohol (p=0.5, p=0.72; respectively). All diabetic patients were classified as having normoalbuminuria (n=54), microalbuminuria, (n=40), and macroalbuminuria (n=6) at baseline. In diabetic patients with low 25(OH)D levels,

normoalbuminuria (n=15), microalbuminuria, (n=12), and macroalbuminuria (n=3) at baseline were found. Mean levels of postprandial glucose in diabetic patients with low 25(OH)D level were statistically significantly higher than that of control.

Table 1. Demographic characteristics of diabetic patients were shown.

Parameters	**Diabetic patients without 25(OH)D deficiency (n= 70)**	**Diabetic patients with 25(OH)D deficiency (n= 30)**	***P***
Age (years)	54.9±11.1	65.4±6.4	*0.63*
Smokers, no (%)	22.0%	30.0%	*0.50*
Smoking pocket/year	21.9±9.1	20.9±2.8	*0.45*
Alcohol consumption, no (%)	20.0%	16.6%	*0.72*
Body Mass Index (kg/m^2)	28.7±6.9	26.3±3.2	0.83
Waist circumference (cm)	107.8±13.4	105.2±8.6	*0.80*
Diabetes duration (years)	8.0±1.0	10.5±3.6	*0.65*
Systolic Blood Pressure (mmHg)	10.1±18.1	125.6±21.5	*0.03**
Diastolic Blood Pressure (mmHg)	67.2±10.0	62.1±17.1	*0.05**

***Data are expressed as mean±SD*

Table 2. Blood profiles of diabetic patients were shown.

	Diabetic patients without 25(OH)D deficiency (n= 70)	**Diabetic patients low 25(OH)D (n= 30)**	***P***
Triglyceride (mg/dl)	140.9±33.1	133.1±47.5	*0.90*
Total-Cholesterol (mg/dl)	249.0±39.4	239.0±46.8	*0.85*
LDL-Cholesterol (mg/dl)	130.9±30.1	125.7±34.8	*0.75*
HDL-Cholesterol (mg/dl)	42.7±10.3	41.2±9.0	*0.40*
Fasting glucose (mg/dl)	133.1±29.4	149.0±39.4	*0.55*
Postprandial glucose (mg/dl)	158.9±50.0	222.2±61.1	*0.001**
A_{1c} (%)	8.4±0.9	7.7±0.77	*0.45*
Urinary albumin excretion (mg/24 h)	37.9±6.0	33.4±2.4	*0.50*
Creatinin (mg/dl)	0.9±0.4	1.0±0.1	*0.60*
Urea (mg/dl)	38.1±4.1	24.1±6.8	*0.90*
25(OH)D (nmol/L)	43.9±3.1	23.9±7.8	*0.03**

** Data are expressed as mean±SD*
Abbreviations: LDL= Low-density lipoprotein; HDL= High-density lipoprotein; 25(OH)D= 25-hydroxyvitamin D

There were statistically significant differences for plasma levels of A1c (p=0.003), postprandial glucose (p= 0.0001), triglyceride (p=0.04), total-Cholesterol (p=0.03), LDL-Cholesterol (p=0.02), and HDL-Cholesterol (p=0.001) between patients with D vitamin supplementation (Table 3). However, no statistically significant difference for urinary albumin excretion levels between before and after treatment was found (p=0.15)

Table 3. Clinical and biochemical characteristics of patients before and after D vitamin supplementation were shown.

	Before supplementation (n= 30)	**After supplementation (n= 30)**	***p***
Body Mass Index (kg/m^2)	26.3±3.2	26.0±3.2	*0.30*
Waist circumference (cm)	105.2±8.6	101.8±9.2	*0.25*
Systolic Blood Pressure (mmHg)	119.8±16.2	125.6±21.5	*0.25*
Diastolic Blood Pressure (mmHg)	61.3±10.3	62.1±17.1	*0.57*
Triglyceride (mg/dl)	133.1±47.5	117.6±22.0	*0.04**
Total-Cholesterol (mg/dl)	239.0±46.8	219.3±47.5	*0.03**
LDL-Cholesterol (mg/dl)	125.7±34.8	119.2±28.0	*0.02**
HDL-Cholesterol (mg/dl)	41.2±9.0	45.3±9.2	*0.001**
Fasting glucose (mg/dl)	149.0±39.4	128.2±25.3	*0.17*
Postprandial glucose (mg/dl)	222.2±61.1	174.8±39.5	*0.0001**
A_{1c} (%)	8.5±1.1	7.7±0.77	*0.003**
Urinary albumin excretion (mg/24 h)	35.1±2.8	33.4±2.4	*0.15*
Creatinin (mg/dl)	1.0±0.1	0.9±0.2	*0.55*
Urea (mg/dl)	24.1±6.8	26.5±6.2	*0.10*
25(OH)D (nmol/L)	23.9±7.8	82.1±16.1	*0.0001**

** Data are expressed as mean±SD*
Abbreviations: LDL= Low-density lipoprotein; HDL= High-density lipoprotein; 25(OH)D= 25-hydroxyvitamin D

In diabetic patients with 25(OH)D deficiency, mean levels of 25(OH)D were negatively correlated with microalbuminuri (r = - 0.802, p = 0.02) and A1c (r = - 0.650, P = 0.001) levels.

Discussion

The extraskeletal health benefits of vitamin D and high prevalence of inadequate levels of vitamin D have been largely unrecognized by both physicians and patients [14- 16]. In the present study, the frequency of 25(OH)D deficiency was found to be 30% in patients with type 2 DM on insulin therapy. And also, 25(OH)D supplementation for 6 months didn't change urinary albumin excretion rate in patients with 25(OH)D deficiency. However, D vitamin supplementation effected mean levels of A1c, postprandial glucose, triglyceride, total-Cholesterol, LDL-Cholesterol and HDL-Cholesterol in diabetic patients with deficiency.

The elderly population is more susceptible to vitamin D deficiency, especially the elderly who live in nursing homes and who are hospitalized [17– 20]. Low 25(OH)D levels are common in patients with both Type 1 and Type 2 diabetes mellitus [21–23]. Similarly, Lee et al. [24] showed that the mean concentration (±SD) of 25(OH)D in patients with type 2 DM was 11.2 (±6.1) ng/ml with a prevalence of Vitamin D deficiency of 85.9%. To our findings, 25(OH)D deficiency was found to be 30% in patients with type 2 DM. In type 2 diabetic patients, severe vitamin D deficiency predicts increased risk of all-cause and cardiovascular mortality, independent of urinary albümin excretion rate and conventional cardiovascular risk factors [2]. Likewise, in the general population, an inverse association was found between vitamin D levels and the prevalence of albuminuria [25]. Previously, sex, body mass index and the use of sun protectors have been shown to be associated with vitamin D deficiency. In a previous study, the prevalence of albuminuria was enhanced with decreased levels 25(OH)D [26]. Similarly, Bonakderon et al. [27] suggested that vitamin D deficiency has a negative effect on albuminuria in diabetic patients, and its replacement might be associated with a beneficial effect on the risk factors of diabetic nephropathy, such as hyperlipidemia and hypertension. In the present study, we found that mean levels of 25(OH)D were negatively correlated with albuminuria in diabetic patients with vitamin deficiency. And also, no effect of D vitamin supplementation on albümin excretion rate was found in diabetic patients with deficiency. There is some evidence that describes the beneficial effect of vitamin D supplement therapy on regulation of blood pressure. Pfeifer et al. [28] demonstrated that supplement therapy with calcium and vitamin D results in better reduction of systolic blood pressure compared with calcium alone. In another study [29], it was found that there was an inverse relation between vitamin D level and blood pressure.

Otherwise, we didn't find any correlations between 25(OH)D levels and systolic or diastolic blood pressures in diabetic patients with D vitamin deficiency. In addition, no effect was found to change blood pressure with D vitamin supplemantation. However, we found that mean levels of triglyceride, total-Cholesterol, LDL-Cholesterol and HDL-Cholesterol significantly changed with D vitamin supplementation. Similarly, Gagnon et al. [30] reported that lower 25(OH)D concentrations were associated with increased metabolic syndrome risk and higher waist circumference, serum triglyceride, fasting glucose, and insulin resistance at 5 year.

Previously, in many studies [31- 33], it was found that there was a relatioship between 25(OH)D level and diabetes risk. Kayaniyil et al [34], suggest that higher plasma 25(OH)D concentrations and higher vitamin D intake are associated with lower risk of type 2 diabetes. To our findings, mean levels of postprandial glucose and A1c improved with D vitamin therapy in diabetic patients with low 25(OH)D level. However, the small number of studies did not allow us to meta-regress baseline 25(OH)D levels against the degree of improvement in glycaemic indices, or to examine whether higher baseline glucose or HbA1c values may have been associated with greater improvements with vitamin D therapy [35, 36]. Future studies related to relationship between glucose control and 25(OH)D level in diabetic patients is needed.

In summary, there were high (30%) frequency of 25(OH)D deficiency in patients with type 2 diabetic patients. And also, D vitamin supplementation changed metabolic parameters such as triglyceride, total-Cholesterol, LDL-Cholesterol and HDL-Cholesterol, postprandial glucose and A1c levels but not albumin excretion rate in patients with low 25(OH)D level.

References

1. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med. 2008;25(3):320–5.
2. Joergensen C, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. Diabetes Care. 2010;33(10): 2238–43.
3. Hypponen E, Power C. Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. Diabetes Care. 2006; 29(10): 2244–6.

4. Kositsawat J, Freeman VL, Gerber BS, Geraci S. Association of A1C levels with vitamin D status in US adults: data from the National Health and Nutrition Examination Survey. Diabetes Care. 2010;33(6):1236–8.
5. Gloth FM, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA. 1995; 274(21):1683-6.
6. Marriott BM. Vitamin D supplementation: A word of caution. Ann Int Med. 1997;127(3):231-3.
7. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am. 2010;39(2):365–79.
8. Kolb H, Mandrup-Poulsen T. An immune origin of type 2 diabetes? Diabetologia. 2005;48(6):1038–50.
9. Pitocco D, Crinò A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, Anguissola GB, Visalli N, Suraci C, Matteoli MC, Patera IP, Cavallo MG, Bizzarri C, Pozzilli P; IMDIAB Group. The effects of calcitriol and nicotinamide on residual pancreatic b-cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI). Diabet Med. 2006;23(8):920–3.
10. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insülin sensitivity in type 2 diabetic patients. Int J Clin Pract. 2003;57(4):258–61.
11. Yilmaz H, Kaya M, Sahin M, Delibasi T. Is vitamin D status a predictor glycaemic regulation and cardiac complication in type 2 diabetes mellitus patients. Diabetes Metab Syndr. 2012;6(1):28-31.
12. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care. 2006;29(3):650–6.
13. Joergensen C, Reinhard H, Schmedes A, Hansen PR, Wiinberg N, Petersen CL, Winther K, Parving HH, Jacobsen PK, Rossing P. Vitamin D levels and asymptomatic coronary artery disease in type 2 diabetic patients with elevated urinary albumin excretion rate. Diabetes Care. 2012;35(1):168-72
14. Barnard K, Colón-Emeric C. Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition. Am J Geriatr Pharmacother. 2010;8(1):4-33.
15. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev. 2005;10(2):94-111.
16. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.
17. Marriott BM. Vitamin D supplementation: A word of caution. Ann Int Med. 1997;127(3):231-3.
18. Gloth FM, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA. 1995;274(21):1683-6.
19. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest. 2005; 35(5):290-304.

20. Hollick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. Am J Clin Nutr. 1994;60(4):619-30.
21. Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract. 1995;27(3):181–8.
22. Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2006;29(3):722–4.
23. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med. 2008;25(3):320–5.
24. Lee JI, Oh SJ, Ha WC, Kwon HS, Sohn TS, Son HS, Cha BY. Serum 25-hydroxyvitamin D concentration and arterial stiffness among type 2 diabetes. Diabetes Res Clin Pract. 2012;95(1):42-7.
25. Joergensen C, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. Diabetes Care. 2010;33(10):2238-43.
26. De Boer IH, Ioannou GN, Kestenbaum B, Brunzell JD, Weiss NS. 25-HydroxyVitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis. 2007;50(1):69-77
27. Bonakdaran S, Hami M, Hatefi A. The effects of calcitriol on albuminuria in patients with type-2 diabetes mellitus. Saudi J Kidney Dis Transpl. 2012;23(6):1215-20.
28. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term Vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab. 2001;86(4):1633-7.
29. Scragg R, Sowers M, Bell C. Serum 25-hydroxy Vitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens. 2007;20(7):713-9.
30. Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Shaw JE, Zimmet PZ, Sikaris K, Ebeling PR, Daly RM. Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). J Clin Endocrinol Metab. 2012;97(6):1953-61.
31. Forouhi NG, Ye Z, Rickard AP, Khaw KT, Luben R, Langenberg C, Wareham NJ. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies. Diabetologia. 2012;55(8):2173-82
32. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of Vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract. 2003;57(4):258-61.
33. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004;79(5): 820-5.

34. Kayaniyil S, Retnakaran R, Harris SB, Vieth R, Knight JA, Gerstein HC, Perkins BA, Zinman B, Hanley AJ. Prospective associations of vitamin D with beta-cell function and glycemia: the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. Diabetes. 2011;60(11):2947–53.

35. Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older US women. DiabetesCare. 2005;28(12):2926–32.

36. Dickinson HO, Nicolson DJ, Cook JV, Campbell F, Beyer FR, Ford GA, Mason J. Calcium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev. 2006;(2):CD004639.