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Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, double-blind, placebo controlled clinical trial

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ABSTRACT

Background: Vitamin D is an important mediator of calcium metabolism. It has also been implicated as a potential contributor to the pathophysiology of various extra-skeletal conditions, consisting hypertension, renal disease, and insulin resistance.

Objectives: The primary objective of this study was to determine whether oral vitamin D (cholecalciferol) supplementation can lead to improvement of blood pressure in type 2 diabetes patients.

Patients and Methods: This study was a double blind clinical trial conducted on 60 type 2 diabetes mellitus patients. Exclusion criteria were taking calcium, vitamin D supplements or any drugs effecting calcium and vitamin D metabolism in the past 6 months. Patients were administered weekly vitamin D supplementation (50000 units) for 12 weeks. Serum 25-Hydroxy vitamin D [25(OH)D] level was measured with ELISA method.

Results: Five patients (8.3%) had vitamin D deficiency, 27 (45%) had insufficient levels of vitamin D and in 28 (45%) patients vitamin D level was within normal limits. The means of systolic blood pressure (BP) and diastolic BP in patients before intervention were 121 and 80.5 mmHg; after intervention they were 110 and 76.3 mmHg, respectively. After intervention, systolic and diastolic blood pressure levels were significantly less than control group ($p< 0.01$).

Conclusions: In this study we found that weekly vitamin D supplementation (cholecalciferol; 50,000 units for 12 weeks) had beneficial effect on the level of blood pressure in type 2 diabetic patients. Thus, oral vitamin D may help in improvement of hypertension in these patients.

Original Article

Implication for health policy/practice/research/medical education:
In this study we found that weekly vitamin D supplementation (cholecalciferol; 50,000 units for 12 weeks) had beneficial effect on level of blood pressure in type 2 diabetic patients. Thus, oral vitamin D may help in improvement of hypertension in these patients.

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1. Introduction

Vitamin D is an important mediator of calcium metabolism. It has also been implicated as a potential contributor to the pathophysiology of various extra-skeletal conditions, consisting hypertension, renal disease and insulin resistance (1). Studies suggest that low 25-hyroxyvitamin D is associated with cardiovascular disease, microalbuminuria, inflammation, diabetes and metabolic syndrome. Studies have shown the worldwide deficiency of vitamin D, however, deficiency of this vitamin has been found a global pandemic for a while and the level of attention given by the scientific and clinical community was only recently stimulated, basically due to the pleiotropic effects of this hormone outside the skeletal system (1-3). Animal studies suggest that low serum 25-hydroxyvitamin D (25[OH]D) may impair insulin synthesis and secretion, and might be involved in the pathogenesis of diabetes (2,3). On the other hand, the global prevalence of type 2 diabetes is growing in parallel to vitamin D deficiency and diabetic kidney disease is a major risk for end-stage kidney disease.

Many complex factors relate to the progression of diabetic kidney disease (1-4). Recently much attention has been directed toward the vitamin D supplementation in diabetic patients while various epidemiological studies have shown associations between low concentrations of 25-hydroxy vitamin D and the incidence of diabetes and its complications (2-4).

Dietary vitamin D supplementation is associated with reduced risk of type 1 diabetes in animals (3,4). Observational studies have shown higher blood pressure trends in winter months, proposing that low ultraviolet radiation and thus decreased capacity for cutaneous vitamin D synthesis are associated with hypertension.

2. Objectives

The primary objective of this study was to determine whether oral vitamin D (cholecalciferol) supplementation could lead to improvement of blood pressure in type 2 diabetic patients.

3. Patients and Methods

3.1. Study population

This study was a randomized, double-blind, placebo controlled clinical trial on 60 patients with the diagnosis of type 2 diabetes referred to endocrinology clinic of Shahrekord University of Medical Sciences in 2011. The patients were allocated into two equal groups of 30 by computer-generated randomly permutated codes (prepared by WHO/Geneva). The inclusion criteria were definite diagnosis of type 2 diabetes according to standard criteria, no kidney or liver disease or any other chronic illness according to the history and physical examinations. Exclusion criteria were taking oral calcium, vitamin D supplements or any drugs effecting calcium or vitamin D metabolism, in the past six months.

3.2. Laboratory tests

First, the blood level of 25-Hydroxy vitamin D [25(OH)D] was measured in all the patients. One group received oral vitamin D (cholecalciferol; 50000 units/week) for 12 weeks, while the other group received placebo for the same period of time. In all patients, fasting blood sugar (FBS), blood sugar (BS), 2 hour postprandial blood sugar (2-hpp) and HbA1c were measured before and after drug therapy. Plasma 25(OH)D was measured with ELISA method by Stat fax 2100 produced by Awareness Company (The United States). HbA1c was measured using column chromatography method with Nyco card reader II made in Norway. FBS, 2-hpp and BS were

measured using spectrophotometer by Erba-XL 300 made in Germany.

3.3. Ethical issues

The research followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was approved by Ethical Committee of Shahrekord University of Medical Science. This study was registered in Iranian Registry of Clinical Trials (IRCT) and achieved the code of IRCT201011185191N6, too.

3.4. Statistical analysis

The data was analyzed with Stata software (Stata Corp. 2011. Stata Statistical Software: Release 12. College Station, TX: Stata Corp LP) using student t-test, paired t-test, Pearson correlation and Chi square tests. P values of less than 0.05 was assumed to be significant ($p<0.05$).

4. Results

A total number of 60 type 2 diabetic patients were randomly assigned into two groups of intervention and control, each group consisting of 30 patients. The intervention group received vitamin D and the control group received placebo. The age of the patients ranged from 34 to 76 with the mean (SD) age of 55 (10.7) years. There was no significant difference for age between groups ($p= 0.88$). Seventeen patients (28.3%) were male. The female to male ratio was not statistically significant ($p= 0.58$). Table 1 demonstrates the laboratory parameters of both groups before and after the intervention.

Means of systolic blood pressure (BP) and diastolic BP in patients before intervention were 121 and 80.5 mmHg; after intervention they changed to 110 and 76.3 mmHg, respectively. After intervention, 25 (OH)D level in interventional group was higher significantly compared to control group. Table 2 demonstrates that after intervention, systolic and diastolic blood pressure levels were significantly less than control group ($p<0.01$).

5. Discussion

The extraskeletal effects of vitamin D have attracted significant interest. There is an abundance of human clinical investigations examining the potential relation between levels of vitamin D metabolites with glycemic control and the incidence of diabetes. In various small supplementation investigations, interventions to increase 25-hydroxyvitamin D has been found to reduce blood pressure in populations at risk of cardiovascular disease (2-5). There is also some evidences that vitamin D supplementation increases pancreatic insulin release and improves, impaired glucose tolerance and insulin resistance in patients with type 2 diabetes. In our study, we found that a short course of vitamin D therapy,

Table 1. Mean (SD) of 25(OH) D (nmol/l) in interventional, control and total groups.

Group	Intervention Group			Control Group			Comparison Between Group P value*	
	Before Mean(SD)	After Mean(SD)	P value	Before Mean(SD)	After Mean(SD)	P value	Interventional	Control
Male	82.5(49)	167.8(32)	0.001*	93.3(67)	94.5(55)	0.83	0.002*	0.971
Female	84.6(54)	162.2(67)	0.001*	109.5(64)	122.2(103)	0.4	0.003*	0.619
Total	83.9(52)	164(57)	0.001*	105.7(64)	115.8(94)	0.39	0.001*	0.632

*P <0.05 comparing the data of each group before and after intervention

Table 2. Mean (SD) of systolic (SYS) and diastolic (DIAS) BP and body mass index in sex groups and total groups

Time of measurement		Intervention Group			Control Group			Comparison Between Group P value*	
Group		Before Mean(SD)	After Mean(SD)	P value	Before Mean(SD)	After Mean(SD)	P value	Interventional	Control
SYS BP	Male	120(13)	113(9.7)	0.006*	117(14)	114(5)	0.522	0.012*	0.05
	Female	121.5(13)	109.5(9)	0.001*	119.3(10)	114.7(10)	0.094	0.001*	0.085
	Total	121(13)	110(9)	0.001*	118.8(11)	114.6(9)	0.06	0.001*	0.09
DIASBP	Male	79.5(9)	77(10)	0.32	80(8)	77(4)	0.35	0.35	0.35
	Female	81(7)	76(6)	0.007*	80.4(7)	79(4)	0.62	0.01*	0.76
	Total	80.5(8)	76.3(7)	0.046*	80.3(7)	79(4)	0.38	0.01*	0.58
BMI (kg/m^2)	Male	27.4(4)	27(4)	0.153	27.4(4)	27(4)	0.153	0.53	0.15
	Female	30.2(4)	30.3(4)	0.731	30.2(4)	30.3(4)	0.731	0.73	0.73
	Total	29.31(4.4)	29.2(4)	0.63	28.8 (4.5)	28.7 (5.2)	0.48	0.73	0.68

*P <0.05 comparing the data of each group before and after intervention

improved the blood pressure in type 2 diabetic patients. Indeed, vitamin D metabolites have been related with the regulation of blood pressure (3-8). Interestingly observational reports have observed higher blood pressure trends in winter months, proposing that low ultraviolet radiation and thus decreased capacity for cutaneous vitamin D synthesis are connected with high blood pressure (2-8). The most noteworthy mechanism associating vitamin D with high blood pressure is its role as a negative regulator of the renin-angiotensin system, other notable hypotheses have suggested that vitamin D affects vascular endothelial function or vascular smooth muscle intracellular calcium concentrations (4-8). Study of Gupta et al, showed that vitamin D level has inverse correlation with circulating renin and angiotensin II, suggesting a mechanism for elevation of blood pressure. Additionally, dietary supplementation with vitamin D appears to reduce blood glucose and blood pressure. It is probable that low serum vitamin D levels elevate the risk for early-stage diabetes and high blood pressure (9).

6. Conclusions

In this study we found that weekly vitamin D supplementation (cholecalciferol; 50,000 units for 12 weeks) had beneficial effect on the level of blood pressure in type 2 diabetic patients. Thus, oral vitamin D may help in improvement of hypertension in these patients.

Authors' contributions

SB and MRK conducted the research. AA analyzed the data. HN prepared the primary draft. MRK edited the manuscript.

Conflict of interests

The authors declared no competing interests.

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