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Original Article

A 3-month oral vitamin D supplementation marginally improves diastolic blood pressure in Saudi patients with type 2 diabetes mellitus

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Abstract: The aim of the current study was to determine whether oral cholecalciferol (45000 IU) per week for the 2 months and once on the 3rd month could translate to full vitamin D status correction and improved metabolic profile among patients with suboptimal vitamin D status. A total of 248 Saudi patients with T2DM were screened for vitamin D deficiency. Two hundred out of the 248 patients had suboptimal vitamin D levels, and were randomly assigned to receive vitamin D oral supplementation (45000 IU/week for 2 months and a single 45000 IU in the last month) or placebo for 3 months. Anthropometrics and fasting blood samples were taken at baseline and after 3 months. Serum glucose, HBA1c and lipid profile were measured routinely and serum 25-OH vitamin D using ELISA. More than half of the subjects (59.8%) were vitamin D deficient at screening. Both groups had significant improvements in vitamin D levels after 3 months, with most of the treatment group achieving status correction. In the treatment group, a significant improvement in the diastolic blood pressure was observed after 3 months (P = 0.021), while the rest of the variables were comparable. Vitamin D supplementation of 45000 IU/week for 2 months and once on the 3rd month was able to improve vitamin D status among vitamin D deficient T2DM patients and marginally improve diastolic blood pressure.

Keywords: Vitamin D supplementation, diabetes mellitus type 2, blood pressure, vitamin D deficiency

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in Saudi Arabia is one of the highest in the world, with more than 30% of Saudi adults having T2DM in Riyadh capital alone [1]. Consequently, accumulating local evidence suggests that vitamin D deficiency, which is also very common in the country, may have contributed in the rise of chronic non-communicable diseases in both children and adults of Saudi Arabia [2-6].

In T2DM, optimum 25(OH) vitamin D levels may improve the cellular transfer of insulin message and may also contribute to the survival of pancreatic islets and inhibit inflammatory processes, with studies that report a relationship between low vitamin D levels in humans and reduced glucose stimulated insulin secretion [7]. In some trials, improvement of insulin release after oral vitamin D supplementation has been observed, but other studies have not confirmed this [8, 9]. Most prospective studies are short term and give variable outcomes about the relationship between vitamin D levels and the subsequent progression to diabetes [10, 11]. Data from the US Third National Health and Nutrition Examination Survey (NHANES III) also showed an inverse association between vitamin D levels and diabetes in non-Hispanic white and Mexican American people but not in non-Hispanic black people [12]. There are four small-scale short-term and two long-term controlled trials that have examined the effects of supplementation with a variety of formulations of vitamin D on T2DM parameters. A study on 18 young healthy men was provided with 1.5 micrograms of oral calcitriol supplementation

per day for 7 days did not change baseline fasting glycemia or insulin sensitivity [13]. In another small study done in Japan (N = 14) in patients with T2DM, 2 micrograms/day of 1 alpha (OH)-vitamin D3 administration daily for 3 weeks enhanced insulin secretion but had no effect on post-load glucose tolerance [14]. Ljunghall and colleagues found no effects on fasting or stimulated glucose tolerance among 65 middle-aged and vitamin D sufficient men with impaired glucose tolerance that were given with 0.75 micrograms alpha-calcidiol daily for 3 months [15]. Prospective studies done in Saudi Arabia on vitamin D status replenishment among patients with T2DM and metabolic syndrome also showed promising effects on cardiometabolic profile and insulin sensitivity, yet the dosages used were either too low or non-pharmacologic treatments were utilized [16-19].

The aim of the present study is evaluate the effect of acute high dose vitamin D supplementation (45000 IU/week) on the glycemic, lipid and anthropometric indices among Saudi patients with T2DM and sub-optimal vitamin D status. Consequently, we aim to determine the prevalence of vitamin D deficiency in the Saudi T2DM cohort.

Patients and methods

Subjects

A sample of 248 adult Saudi patients with T2DM were recruited from the out-patient Diabetes Clinics in Family Medicine and Primary Health Care at Health Care Specialty Clinic (HCSC)-King Abdul-Aziz Medical City in Riyadh, Saudi Arabia last from July 2010 to March 2011. HCSC is a primary care and family medicine center, located at northeastern part of Riyadh. It services the soldiers and their dependents that belong to its catchments areas. All subjects were requested to answer a generalized questionnaire which included demographic data, duration of diabetes mellitus, co-morbid diseases, type of anti-diabetic medications (diet only, oral hypoglycemic agents (OHA) or insulin), and frequency of sun exposure as well as consumption of dairy products and poultry. Patients with renal insufficiency, gestational diabetes, on vitamin D supplements and those most likely to change their course of medications within 3 months were excluded. Written informed consents were obtained prior to inclusion. Ethical approval was obtained from the Institutional Review Board (IRB) in King Abdullah International Medical Research Center prior to study commencement.

Anthropometric and clinical measurements

All subjects were given appointments after screening for baseline measurement of anthropometrics and fasting blood extraction. Anthropometrics were measured and included height (cm) and weight (kg) using standardized stadiometers and weighing scales, respectively, as well as systolic and diastolic blood pressure using mercurial sphygmomanometer. Fasting blood samples were obtained from all 248 patients to determine fasting blood glucose, HBA1c and lipid profile using routine laboratory methods. Total serum 25(OH) vitamin D was measured using the LIAISON® 25 OH Vitamin D TOTAL assay, from DiaSorin, USA. T2DM patients with suboptimal vitamin D status (< 75 nmol/l) were considered eligible to participate in the interventional phase the study. Patients with normal vitamin D levels (N = 48) (≥ 75 nmol/l) were excluded but results were utilized to determine the prevalence of vitamin D deficiency in the entire cohort. Eligible patients were then allocated into groups and were followed up for 3 months for repeat measurements of anthropometrics and fasting blood indices. Out of the 200 subjects who started, 183 subjects (N = 91 treated, N = 92 control) were able to complete the intervention. Given the good response rate, per-protocol analysis was employed.

Randomization

Patients were randomized to treatment or control groups using sequentially numbered, opaque sealed envelopes. All envelopes were pooled in a plastic container. One clinical nurse, not in direct contact with patients or physicians, was assigned for the randomization process. Each patient on their 2nd visit was asked to pick up an envelope for the allocation of treatment. Envelopes which contain the letter T (treatment) were placed in the treatment arm and was given vitamin D supplements in the form of cholecalciferol 45000 I.U. orally once every week for 2 months and a single 45000 I.U. in the last month, as recommended by National Guideline Clearinghouse (www.guide-

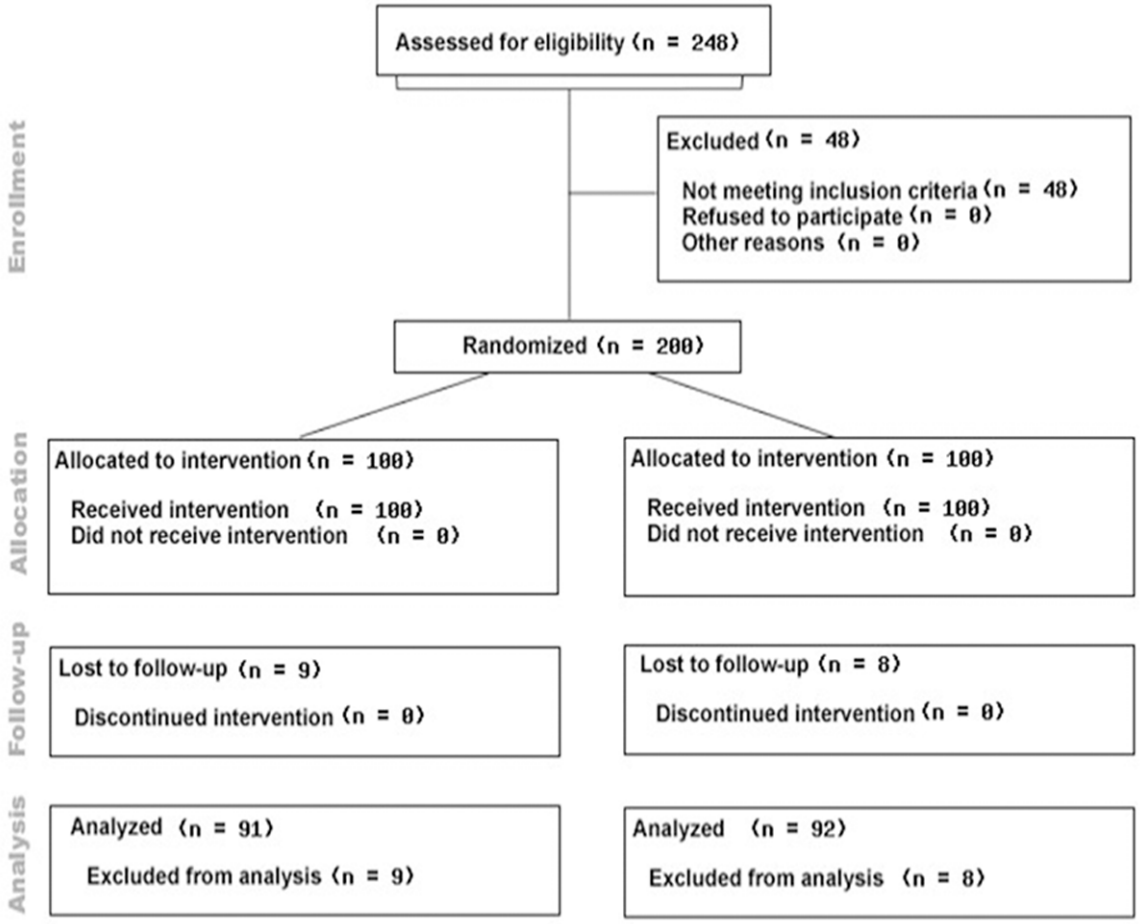

Figure 1. Flow diagram of the interventional study.

line.gov). On the other hand, patients with envelopes that contain the letter C (control) were considered to belong in the control group and were given counseling on non-pharmacologic ways of replenishing vitamin D status (e.g., increased sunlight exposure, increased dietary intake of vitamin D-rich foods). **Figure 1** shows the flow diagram of the study.

Data analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were presented as mean ± standard deviation and frequencies were presented as percentages (%). Chi-square test was applied for testing the association and/or difference between categorical variables. Paired t-test was used to compare means of quantitative variables at baseline and after intervention separately for each arm group. Student T-test was used to compare means between treatment and control group. Significance was set at $P < 0.05$.

Power size calculation was also done using G*Power software. Using the mean and standard deviation values of diastolic blood pressure in the T2DM group at baseline and after 3 months intervention, given alpha = 0.05 and a power of 0.80, a sample size of N = 72 per arm is required to observe a difference between two dependent means (matched pairs). The present sample size of N = 91 per arm has a power of 0.89 given alpha = 0.05.

Results

More than half of the 248 subjects (59.8%) were vitamin D deficient (< 50 nmol/L), 96 patients 38.6% (N = 96) had vitamin D insufficiency (50-74.9 nmol/L) while only 4 patients (1.6%) had optimum vitamin D levels (> 75 nmol/L). Furthermore, the female subjects had

Table 1. Demographic characteristics of subjects

	Treated	Control	*P*-Value
N	91	92	
Age (years)	56.9 ± 9.4	52.5 ± 8.1	0.001
Gender (M/F)	56/35	33/59	0.001
Marital Status			
Married	84 (92.3)	87 (94.6)	0.56
Divorced	7 (7.7)	5 (5.4)	
Educational Status			
Illiterate	37 (40.7)	56 (60.9)	0.006
Elementary	37 (40.7)	16 (17.4)	
Intermediate	12 (13.2)	15 (16.3)	
≥ Secondary	5 (5.5)	5 (5.4)	
Medical History			
Co-Morbid Diseases	76 (83.5)	75 (81.5)	0.85
Hypertension	51 (67.1)	45 (60.0)	0.40
Dyslipidemia	59 (77.6)	54 (72.0)	0.46
Vitamin D status			
Deficiency	56 (61.5)	59 (64.1)	0.42
Insufficiency	35 (38.5)	33 (35.9)	
DM Treatment			
Diet only	1 (1.1)	0 (0)	0.004
OHA*	67 (75.3)	76 (82.6)	
Insulin	21 (23.6)	9 (9.8)	
OHA and insulin*	0 (0)	7 (7.6)	
Sun exposure and diet			
Sun exposure			
Never	3 (3.4)	3 (3.4)	0.97
Sometimes	70 (79.5)	72 (80.9)	
Regular	15 (17.0	14 (15.7)	
Dairy product intake			
Never	5 (5.7)	5 (5.6)	0.79
Sometimes	68 (77.3)	66 (73.3)	
Regular	15 (17.0)	19 (21.1)	
Egg/fish intake			
Never	10 (11.5)	3 (3.3)	0.08
Sometimes	25 (28.7)	34 (37.8)	
Regular	52 (59.8)	53 (58.9)	

Note: Data presented as mean ± standard deviation or frequency (%); *OHA (Oral Hypoglycemic agents); *P*-value significant at < 0.05.

significantly higher prevalence of vitamin D deficiency than males (73.6% versus 46.9%; $P < 0.001$) (not shown in table).

Table 1 shows the demographic characteristics of subjects. Subjects in the control group were significantly younger than the treatment group ($P = 0.001$). The control group also had more females ($P = 0.001$), with a higher prevalence of illiteracy (P = 0.006) and OHA with insulin use ($P = 0.004$) than the treatment group. No differences were observed in medical history, sun exposure and diet (**Table 1**).

The metabolic profile of both groups at baseline and after intervention are shown in **Table 2**. Both the treatment and the control group had significant improvements in 25-OH vitamin D levels after 3 months from baseline values, with most of the treatment group achieving status correction. In the control group, all the rest of the parameters, with the exception of 25-OH vitamin D, were essentially the same after 3 months. However in the treatment group, a significant improvement in the diastolic blood pressure was observed after 3 months ($P = 0.021$), while the rest of the variables were comparable. **Figure 2** shows the significant increase in the number of vitamin D sufficient subjects in the treatment group as compared to control group after 3 months of intervention (83.1 versus 7.7; *P*-value 5.3×10^{-6}).

Discussion

The present study was designed to determine whether an acute high-dose vitamin D supplementation will translate to improved glycemic and metabolic profile among T2DM patients with sub-optimal vitamin D levels. The results did not show significant changes in glycemic control in treated patients after using cholecalciferol 45000 I.U. orally once every week for 3 months. Jorde and Figenschau also reported no significant effects on glycemic control in subjects with T2DM without vitamin D deficiency after vitamin D3 supplementation (40,000 IU per week) for 6 months. In this study, a small sample size (36 subjects) with T2DM, treated with metformin and bed-time insulin, were randomized to cholecalciferol supplementation (40,000 IU per week) versus placebo for 6 months [20]. Furthermore, Patel, et al studied subjects with T2DM and serum 25-OH vitamin D concentrations < 25 ng/mL. They were randomized to receive 400 IU (Group 1) or 1200 IU (Group 2) cholecalciferol for 4 months. The mean 25(OH) vitamin D levels increased in both groups (from 17.6 ± 1.5 to 25.5 ± 1.8 ng/mL in group 1 and from 15.6 ± 1.4 to 27.4 ± 2.4 ng/mL in group 2; $P \leq 0.001$ versus baseline for each group). No significant differences were noted in fasting plasma glucose and HbA1c compared with baseline within groups or between the two groups [21].

Table 2. Anthropometric, glycemic, lipid and vitamin D status of subjects at baseline and after 3 months

N	Treatment Group		Control Group	
	91		92	
	Baseline	After 3 Months	Baseline	After 3 Months
Anthropometrics				
BMI (kg/m^2)	31.3 ± 4.6	31.6 ± 4.8	32.0 ± 5.7	32.5 ± 6.1
Systolic Blood Pressure	123.4 ± 15.8	122.4 ± 15.4	124.0 ± 15.4	124.0 ± 15.1
Diastolic Blood Pressure	76.4 ± 10.8	73.2 ± 7.2*	75.3 ± 9.2	73.7 ± 7.7
Glycemic Profile				
Fasting Glucose (mmol/l)	9.6 ± 3.7	9.3 ± 3.1	9.4 ± 3.0	10.0 ± 3.7
HbA1C (%)	8.5 ± 1.6	8.6 ± 1.6	8.6 ± 1.7	8.7 ± 1.8
Lipid Profile				
Triglycerides (mmol/l)	1.8 ± 0.99	1.8 ± 0.92	1.7 ± 0.92	1.6 ± 0.8
Total Cholesterol (mmol/l)	4.2 ± 0.95	4.2 ± 0.92	4.3 ± 0.94	4.3 ± 0.9
HDL-Cholesterol (mmol/l)	1.0 ± 0.2	1.0 ± 0.2	1.01 ± 0.23	1.02 ± 0.2
LDL-Cholesterol (mmol/l)	2.5 ± 0.8	2.5 ± 0.8	2.6 ± 0.83	2.6 ± 0.7
Vitamin D Status				
25-OH Vitamin D (nmol/l)	25.3 ± 15.8	82.8 ± 31.7**	22.0 ± 15.2	55.0 ± 37.8**

Note: Data presented as mean ± standard deviation; *denotes significance at 0.05 level; **denotes significance at 0.01 level; significance at $P < 0.05$.

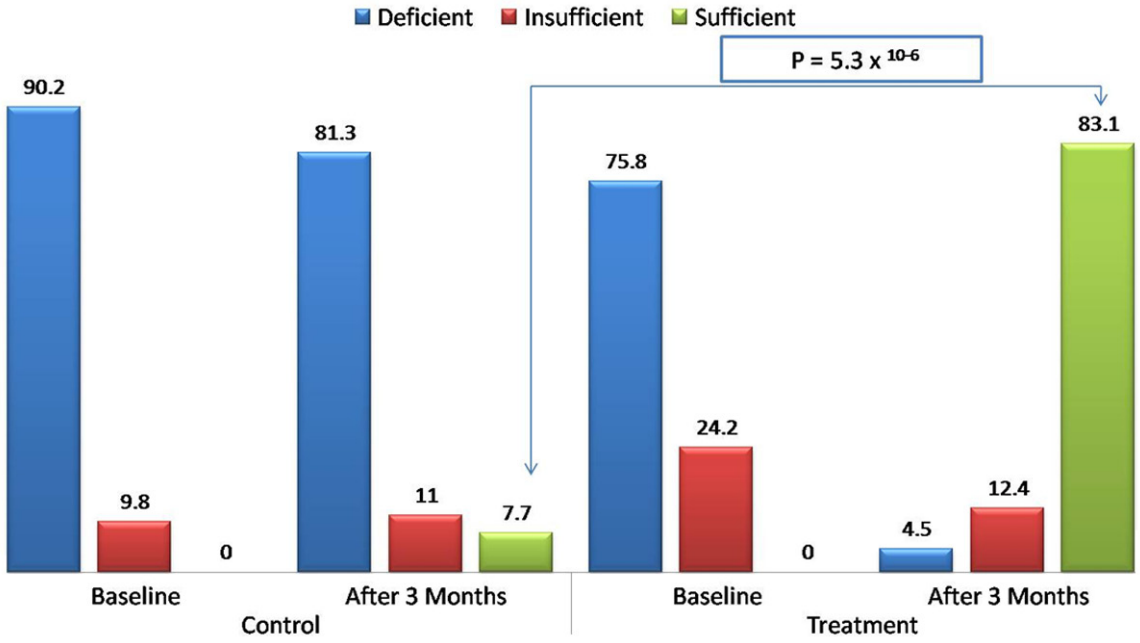

Figure 2. Vitamin D status deficient (< 50 nmol/l), insufficient (50-74.9 nmol/l) and sufficient (≥75 nmol/l) of control and treatment groups at baseline and after 3 months.

The results of the present study are in contrast to the findings of Al-Daghri et al., which observed several cardiometabolic benefits including improved insulin sensitivity even from modest increments in circulating 25-OH vitamin D levels [18, 19]. Several factors could be attributed to this. First, the 2 studies have a longer follow-up duration as compared to the present study despite the lower dosage of vitamin D supplementation given. The 3 month

duration in the present study maybe enough to significantly correct vitamin D status of most patients in the treatment group and some in the control, but may have been too short to manifest any modest improvement in the measured variables, including HBA1c which is routinely recommended to be measured every 3-4 months. Second was the lack of other indices in the present study such as insulin, HOMA-IR and HOMA-β which might show some changes even in acute interventions. Lastly, there is discrepancy in the confounding variables accounted for in the former studies not included in the present one such as season for vitamin D and physical activity which greatly influences cardiometabolic variables measured in this study.

In the current study, it was observed that supplementation with cholecalciferol did not lead to significant reductions in total weight or change in BMI. There were few previous studies reporting the effect of vitamin D supplementation on weight, and the results are conflicting. In a study by Ljunghall et al. on 65 men aged 61-65 years, a significant weight loss of 1.1 kg was observed in the treatment group after 12 weeks given 0.75 mg alphacalcidol than the placebo group [22]. Similarly, in a long-term study of 18 months, Lind et al. observed that alphacalcidol caused a small but significant weight loss (0.9 kg) in a group of 14 middle-aged men [23]. On the other hand, treatment for 1 year with either 2000 IU cholecalciferol, 0.25 mg alphacalcidol, or 0.25-0.50 mg calcitriol had no effect on body weight when compared with placebo among 238 post-menopausal women [24]. Furthermore, in a recent study by Trivedi et al. on men and women aged 65 years or above, cholecalciferol in a dose of 100000 IU or placebo was given every 4 months and, in a subgroup analysis on 238 subjects, there was no significant difference in body weight between the two groups after 5 years [25]. In view of the two latter studies, together with our findings, we consider it highly unlikely that supplementation with cholecalciferol has a major effect on weight. This is also supported by a recent study where a 2000 IU cholecalciferol daily for 7 days among ten healthy young men had no effects on weight and fat metabolism [26].

The marginal significant effect on the diastolic blood pressure in the treatment group should be interpreted with caution since longer intervention trials did not observe the same significant improvement in blood pressure [27, 28]. Several factors such as different ethnicities, genetics and study design may all contribute to conflicting results. As such, the significant improvement in the diastolic blood pressure needs confirmation. It is worthy to note however that circulating 25(OH) vitamin D is known to exert effects in the renin-angiotensin system, but how it plays out clinically warrants further investigation [29].

The authors acknowledge several limitations. The acute duration of the study has probably limited any apparent changes despite full correction of vitamin D status. Furthermore, diet, season and physical activity were not accounted for. Baseline characteristics of the original cohort (N = 200) were unfortunately not provided and as such may cast doubt in the randomization procedure. Nevertheless, the study has considerable strengths which include a very good response rate (91.5%) and the first interventional study in the region to observe the acute metabolic effects of full vitamin D status correction among Arab patients with T2DM.

In summary, full vitamin D correction did not significantly improve glycemic indicators, BMI and lipid profile of Saudi T2DM patients with the exception of diastolic blood pressure which was marginal and apparent only in the treated group. Longer prospective studies are needed utilizing the same dosage to confirm whether or not vitamin D status correction can be used as an adjuvant therapy for patients with T2DM.

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Disclosure of conflict of interest

None.

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