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RESEARCH ARTICLE

Effect of vitamin D therapy on bone mineral density in patients with diabetic nephropathy; a randomized, double-blind placebo controlled clinical trial

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Abstract

Purpose Diabetes compromises bone strength resulting increased risk of osteoporosis. Objective of this study was to determine the effect of vitamin D given to patients with early diabetic renal disease on BMD and BMC.

Methods Patients with diabetic nephropathy were recruited. Treatment group received 50,000 IU of vitamin D3 intramuscularly and the control group was given an equal volume of distilled water (0.25 mL) monthly for six months. Baseline BMD, BMC in the total body, lumbar spine and proximal femur were measured by DXA. After six months measurements were repeated. When trial period was over, a randomly selected subgroup of patients (25 from each group) was followed up for further six-months and measurements were repeated.

Results Selected patients were randomly assigned to two groups. After six months, the treatment group total body BMD, total body BMC and BMDs of spine, femoral neck and total hip regions increased by 2.0%, 2.2%, 1.8%, 2.1% and 2.6% ($P < 0.05$ for all within-group differences), respectively. In the Control group, BMD or BMC of any region mentioned above did not change significantly during the initial 6 months ($P < 0.05$ for the between-groups differences). After 6 months of stopping treatment, a statistically significant reduction of total BMD and BMC was observed in the treatment group ($P = 0.009$).

Conclusion This study showed that treatment with high dose vitamin D significantly influences total body BMC, total body BMD, BMDs of spine, femoral neck and hip among patients with diabetic nephropathy.

Keywords Bone mineral density · Diabetic nephropathy · Vitamin D

Purpose

Diabetes compromises bone strength resulting increased risk of osteoporosis [1, 2]. Bone mineral density (BMD) which is a surrogate of bone strength is lower in type 1 diabetes. The association between BMD and type 2 diabetes, however, has been inconsistent [3–6]. Hyperglycemia, hypercalciuria and impaired renal function are the plausible explanations for the reduced bone quantity in diabetes [7].

Vitamin D has proven efficacy in postmenopausal and glucocorticoid-induced osteoporosis [8–10]. According to a Cochrane review, calcitriol therapy prevents bone loss at lumbar spine and forearm by about 3% after one year of treatment in postmenopausal women [11]. Severe vitamin D deficiency in patients with chronic kidney disease is a well-known fact [11, 12].

We were unable to find studies that examined the effect of vitamin D on BMD among subjects with early diabetic nephropathy. It is unlikely that renal failure of this degree derange vitamin D metabolism [13].Many studies have shown that hypovitaminosis is prevalent among healthy middle aged women in South Asia [14]. Therefore, this study was conducted to determine, the effect of vitamin D therapy on BMD involving patients with early diabetic nephropathy which was the secondary outcome of this study. Primary outcome of this study was to examine the effects of vitamin D therapy on renal functions of patients with diabetic nephropathy (DN).

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Methods

Patients attending adult medical clinics in Teaching Hospital, Karapitiya, Galle were screened for those with early diabetic nephropathy (defined as albumin creatinine ratio (ACR) >30 mg/g and estimated glomerular filtration rate (eGFR) more than 30 mL/min). Based on history and physical examination other causes of albuminuria were excluded before assessing their urine for microalbuminuria. Patients who had albuminuria in the initial assessment underwent second urine assessment within two months to confirm the presence of albuminuria. This procedure ensured confirmation of albuminuria which was an inclusion criterion of the study. Informed written consent was obtained from all participants and the study was registered in the National Clinical Trial Registry (Registration No: SLCTR/2009/008). Subjects with uncontrolled blood pressure (>130/80 mmHg over the last two clinic visits), hyperphosphataemia (Serum phosphate >5 mg/dL), hypercalcaemia (Serum total Ca > 10 mg/dL), uncontrolled blood sugar (HbA1c > 8%) chronic liver disease, hyperthyroidism, hyperparathyroidism, decompensated heart failure or diseases related to calcium or vitamin D metabolism were excluded.

A total of 157 people were invited for the study and 72 were excluded due to the presence of one or more exclusion criteria. Remaining 85 were randomly assigned to two groups; 43 subjects in the treatment group and 42 subjects to the control group.

The variables in this study were as follows; GFR was estimated by the Cockroft-Gault equation, ACR (Albumin Creatinine Ratio), BMD (Bone Mineral Density) and BMC (Bone Mineral Content).

Table 1 shows the study visits, the measurements obtained and the interventions done in each visit.

Study design

Participants were allocated to two groups by Block randomization method (block of 2) using a computer-generated random number table. Concealed envelopes containing treatment allocation were given to research assistants who assigned participants to treatment and control groups. Treatment group received a monthly dose of 50,000 IU of vitamin D3 intramuscularly and the control group was given an equal volume of distilled water (0.25 mL) to the same site in the similar manner. The drug was given by separate group of research assistants. Participants, those administering the intervention, clinicians, and outcome assessors were blinded to the group assignment.

Study procedures

Samples of blood and urine were collected from all participants at the baseline for biochemical analyses. Urine albumin was determined by turbidimetric method. Urinary creatinine concentration was determined using an end-point spectrophotometric method with an alkaline-pictrate solution. Biochemical assays were performed using commercial kits. Intact PTH (Immunotech, IRMA PTH), rennin (Beckman coulter, IRMA Active Renin) by radioimmunoassay and 25-hydroxy vitamin D were measured using immunochemiluminometric (Vitros immunodiagnostic) assays. Serum creatinine was measured by spectrophotometric method with an alkaline-pictrate solution. The automated data reduction technique was used to calculate serum vitamin D3 result. All underwent whole body dual-energy X-ray absorptiometry (DXA) scan and BMD and BMC of the total body, total spine (L1-L4) and proximal femur were measured.

All scans were performed and analyzed by the same technician adhering to the manufacturer's protocol. DXA machine was calibrated on each scan day using the calibration phantom provided by the manufacturer. The DEXA machine used in this study has precision errors of 0.008 g/cm^2 in different Regions of Interest. There was no change of either software or hardware of the DXA machine during the study period.

Participants received either vitamin D3 or placebo injections once the baseline measurements were completed. A safety visit was scheduled after one week of the first injection to monitor serum Ca and phosphorus concentrations and to elicit possible adverse events. The protocol specified withdrawal from the trial if serum Ca exceeded 11 mg/dL. After six months of treatment all the measurements done at the baseline including DXA were repeated. When the trial period of six months was over, a randomly selected subgroup of participants (total of 50 and 25 from each group) was followed up for further six months and another DXA measurement was performed.

Table 1 Details of study visits and measurements and interventions done in each visit

Timing of the visit	Measurements obtained
Baseline	PTH, vitamin D level, serum calcium, serum creatinine, and BMD and BMC
One week	Serum calcium
Six months	PTH, vitamin D level, serum calcium, serum creatinine and BMD
One year	BMD in 25 patients from each group

Statistical analysis

The baseline characteristics between the groups were compared using either unpaired t-test or the Chi-square test. Differences in BMD and BMC` before and after six months of treatment was analyzed by the repeated measure analysis of variance (ANOVA) (SPSS, Chicago, USA). Differences in bone mineral density, before and after vitamin D treatment, was analyzed by repeated measure ANOVA (within and between group variations). All the participants randomized were included in the analysis regardless of the follow-up (Intension- to-treat method) and *p* values were adjusted for multiple comparisons.

Results

Baseline characteristics of the participants are listed in Table 2. No significant differences were found with regard to the baseline characteristics between the treatment and control groups.

Four participants from each of the groups did not complete the study. They were not contactable due to the change of the residence. At the end of six months DXA results were available in 39 participants in the treatment group and 38 in the control group. At the end of one year, 25 from each group underwent the 3rd BMD measurement.

Table 3 shows the changes of the total body BMD and BMC, regional BMDs, total fat and lean masses, during the initial 6 months of treatment in the treatment and control groups.

After six months of vitamin D injections, total body BMD, total body BMC and BMDs of spine, femoral neck and total hip region increased by 2.0%, 2.2%, 1.8%, 2.1% and 2.6% ($P < 0.05$ for all within-group differences), respectively from the baseline figures. However, increase observed in the trochanteric BMD among them was not statistically significant. In the control group, compared to the baseline, total body BMC, BMD, and regional BMDs did not change significantly during the initial six months (Fig. 1).

Table 4 shows the changes observed in the BMD measurements six months after stopping treatment in the two subgroups followed up.

Six months after the cessation of vitamin D treatment, significant reductions of both total BMD and BMC were observed ($P = 0.009$) while regional BMDs remained unchanged. In the control group none of the BMD and BMC measurements changed significantly during the post-trial follow up six months period.

Mean vitamin D level of participants in the treatment group was not significantly different from that of the control group and only 12 subjects in the treatment group had their vitamin D levels below 50 nmol/L cut-off value at the baseline.

Discussion

In this randomized, double-blind, placebo-controlled clinical trial, we observed several changes in the treatment group. There was a significant increase in total body BMD, BMC

Table 2 Descriptive data of the participants in the test and control groups

Variable	Control (n=43)	Treatment (n=42)	P value
Age	59 (8)	56 (10)	0.1
Number of males (%)*	18 (41.8)	20 (47.6)	0.58
Calcium (mg/dL)	8.9 (0.7)	8.8 (0.6)	0.65
Phosphorus (mg/dL)	3.8 (0.6)	3.9 (0.5)	0.31
PTH (pg/mL)	42.5 (19.0)	38.2 (11.3)	0.21
25(OH)D (nmol/L)	50.0 (16.5)	55.9 (12.3)	0.07
FBS (mg/dL)	130.2 (12.5)	128.4 (13.3)	0.51
Duration of diabetes (years)	7 (4)	8 (5)	0.42
Total body BMD (g/cm^2)	1.04 (0.12)	1.038 (0.12)	0.96
Total body BMC (g)	1775.63 (412.76)	1757.95 (383.68)	0.84
Spine BMD (g/cm^2)	0.848 (0.132)	0.845 (0.153)	0.92
Femoral neck BMD (g/cm^2)	0.722 (0.109)	0.731 (0.153)	0.76
Trochanter BMD (g/cm^2)	0.607 (0.089)	0.615 (0.111)	0.72
Total hip BMD (g/cm^2)	0.857 (0.113)	0.876 (0.148)	0.52
Total fat mass (kg)	15.85 (6.67)	17.41 (5.37)	0.24
Lean mass (kg)	37.04 (6.94)	38.92 (8.32)	0.27

PTH (parathyroid hormone), FBS (fasting blood sugar), BMD (bone mineral density), BMC (bone mineral content)

* as a percentage and others are as SDs

Table 3 Changes bone mineral density and fat mass in the treatment and control groups

Variable		Baseline	After 6 months	Percentage difference	P within groups	P between groups
BMD (g/cm^2)	Control	1.038 (0.121)	1.031 (0.191)	−0.67	0.75	0.61
	Treatment	1.038 (0.120)	1.059 (0.107)	2.02	0.01	
BMC (g)	Control	1775.63 (412.76)	1721.64 (369.70)	−3.04	0.074	0.73
	Treatment	1757.95 (383.68)	1795.85 (373.27)	2.16	0.007	
Spine BMD (g/cm^2)	Control	0.848 (0.132)	0.836 (0.119)	−1.41	0.27	0.72
	Treatment	0.845 (0.153)	0.860 (0.142)	1.78	0.04	
Femoral neck BMD (g/cm^2)	Control	0.722 (0.109)	0.712 (0.094)	−1.38	0.23	0.43
	Treatment	0.731 (0.153)	0.746 (0.142)	2.05	0.03	
Trochanter BMD (g/cm^2)	Control	0.607 (0.089)	0.604 (0.08)	−0.49	0.5	0.46
	Treatment	0.615 (0.111)	0.627 (0.103)	1.95	0.07	
Hip BMD (g/cm^2)	Control	0.857 (0.113)	0.852 (0.105)	−0.58	0.56	0.25
	Treatment	0.876 (0.148)	0.899 (0.149)	2.62	0.008	
Total fat mass (kg)	Control	15.85 (6.67)	16.48 (6.16)	3.99	0.20	0.2
	Treatment	17.41 (5367.460)	18.21 (5.56)	4.6	0.06	
Lean mass (kg)	Control	37.04 (6.94)	36.98 (6.38)	−0.18	0.86	0.16
	Treatment	38.92 (8.32)	39.64 (7.73)	1.85	0.09	

BMD (bone mineral density), BMC (bone mineral content)

and BMDs at the total spine, femoral neck and total hip areas after six months of monthly intramuscular vitamin D injections. Vitamin D treatment resulted in nearly 2% increase in the total and regional BMDs during the study period of six months. Furthermore, BMDs in skeletal sites which are clinically relevant remained unchanged six months after withdrawing the treatment. BMDs at the total body and BMC, however, declined, marginally, after withdrawing the treatment. The between group differences, however, were not significant, possibly due to small sample size and shorter duration of the study. We suggest further trials in this area with more subjects and longer follow up.

There are many plausible explanations for the skeletal benefits of vitamin D treatment observed in this treatment group. It could partly be related to vitamin D deficiency among participants of the study at the baseline. Patients with hypovitaminosis D may have shown an exaggerated BMD response to vitamin D and this may have contributed to the nearly 2% increase in the mean BMD after 6 months. Mean vitamin D level of participants in the treatment group was not significantly different from that of the control group and only 12 subjects in the treatment group had their vitamin D levels below 50 nmol/L cut-off value at the baseline. Furthermore, there was no association between the baseline vitamin D level and the BMD response among subjects in the study group ($r = 0.15$, $P > 0.05$) to indicate a possible regression to mean effect. Furthermore, BMD and BMC trends were similar among subjects with low vitamin D and normal vitamin D in the treatment group.

It can be argued that the observed BMD and BMC increase could result from the precision error associated with BMD measurements. The DXA machine used in this study has a precision error of 0.008 g/cm^2 in different Regions of Interest [15]. At the precision error of this magnitude, the Least Significant Change of 4–5% can be expected and the observed BMD difference falls below this [15]. The Least Significant Change, however, is applicable only when the replicate BMD measurements of an individual participant are compared and it is not applicable when group data (mean values) are compared. Many major clinical trials in the field of postmenopausal osteoporosis consider similar mean BMD differences to be statistically significant and clinically important [16, 17].

BMD and BMC can increase over time due to age-related changes. This occurs as a result of progressive degenerative changes in the skeleton and calcification of the major arteries close to the Regions of Interest. This is an unlikely explanation as the study period was short and no increase in the BMD or BMC was seen among subjects in the control group.

We were unable to find previous studies of similar nature where effects of vitamin D have been tested in patients with early diabetic nephropathy. Most of the studies have been conducted on patients with renal failure due to other causes and also in their disease in advanced stage. They either had secondary hyperparathyroidism or were on renal replacement therapy and some were renal transplant recipients [18–20]. Drugs that were tested include bisphosphonates, calcimimetics and vitamin D derivatives [21–23]. Our study sample was different from those above as participants in the current study had normal serum creatinine, therefore, unlikely to have either secondary hyperparathyroidism or vitamin D deficiency secondary to poor renal conversion of 25 OH D to 1, 25 (OH)2 vitamin D.

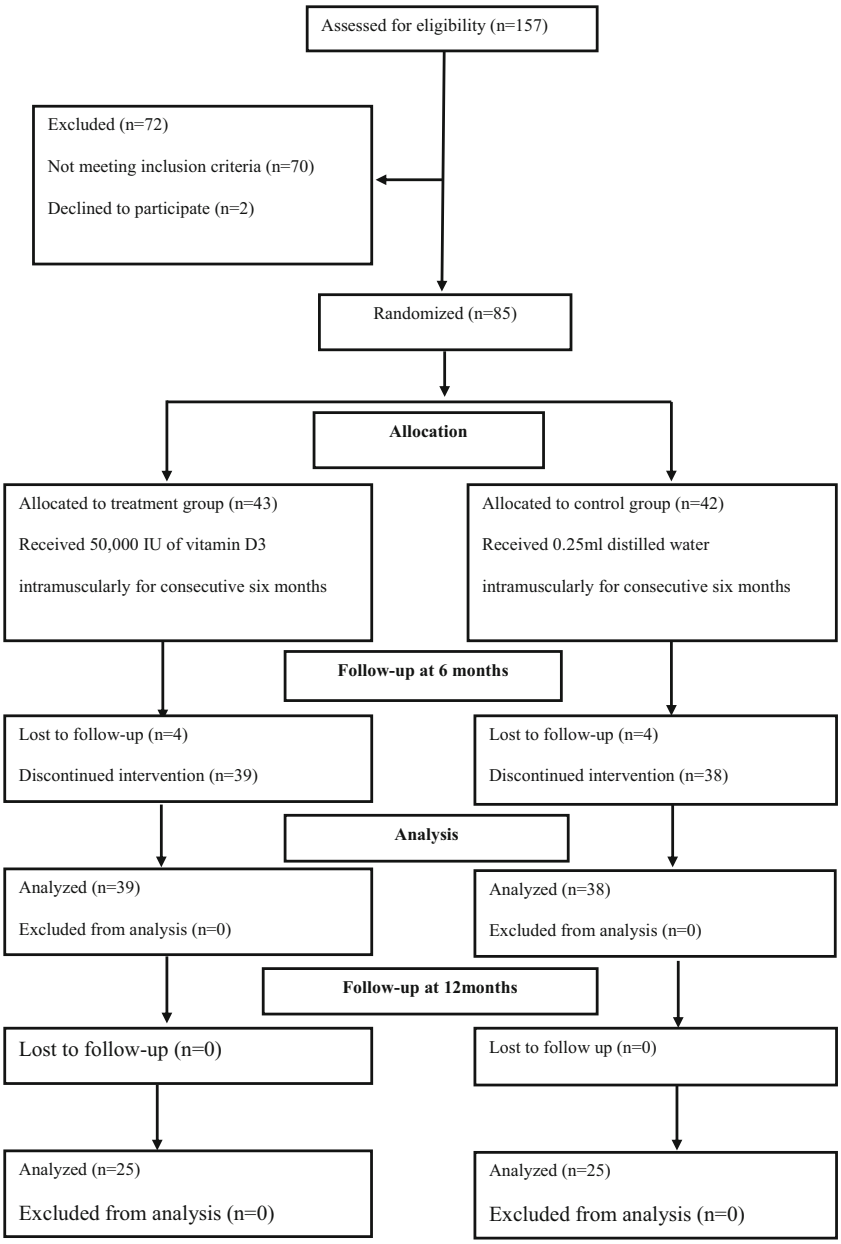

Fig. 1 flow diagram of the recruitment of the patients for the study

Beneficial effects of vitamin D in people with low BMD are well established. It is recommended to co-prescribe a daily dose of 800 IU of vitamin D3 together with all specific osteoporosis treatment in postmenopausal osteoporosis. In a meta-analysis, vitamin D given in excess of 800 IU per day reduced both hip and non-hip fractures among postmenopausal women [8]. Furthermore, according to a Cochrane review, vitamin D can preserve BMD in long term glucocorticoid users and vitamin D is widely recommended for these patients.

The benefits of vitamin D is possibly dose related. Especially pleiotropic effects of vitamin D are evident only at higher serum levels of vitamin D. In this study we were able to give a higher dose of vitamin D to the participants. The dose that we used did not cause major adverse effects or hypercalcaemia.

There are several limitations in this study. Treatment period is possibly too short to show the full effects of vitamin D on bone tissue. Not performing radiographs to detect prevalent or incident vertebral fractures and not gathering data on fractures are other limitations of our study.

Major strength of this study is that it employed a proper method of randomization to achieve treatment and control groups with similar characteristics at the baseline. Further, blinding of all people who could influence the outcome measurement and concealment of treatment allocation were also strengths of our study. Bioavailability issues and compliance

Table 4 Changes in BMD, BMC and fat and lean masses in the treatment and control groups during the follow up period

Variable		After 6 months	After 12 months	Percentage difference	P within groups	P between groups
BMD (g/cm^2)	Control	0.999 (0.134)	1.006 (0.112)	0.70	0.47	0.21
	Treatment	1.054 (0.120)	1.041 (0.131)	−1.23	0.009	
BMC (g)	Control	1735.92 (430.22)	1716.05 (402.87)	−1.14	0.26	0.54
	Treatment	1808.19 (450.57)	1795.94 (458.27)	−0.68	0.04	
Spine BMD (g/cm^2)	Control	0.823 (0.128)	0.828 (0.126)	0.61	0.19	0.69
	Treatment	0.847 (0.168)	0.837 (0.163)	−1.18	0.07	
Femoral neck BMD (g/cm^2)	Control	0.711 (0.109)	0.711 (0.105)	0	0.92	0.28
	Treatment	0.756 (0.166)	0.753 (0.169)	−0.4	0.48	
Trochanter BMD (g/cm^2)	Control	0.601 (0.823)	0.598 (0.851)	−0.5	0.35	0.55
	Treatment	0.617 (0.112)	0.615 (0.110)	−0.32	0.33	
Hip BMD (g/cm^2)	Control	0.851 (0.114)	0.848 (0.116)	−0.35	0.69	0.3
	Treatment	0.889 (0.160)	0.895 (0.160)	0.67	0.48	
Total fat mass (kg)	Control	16.10 (6.75)	15.66 (6.57)	−2.71	0.06	0.22
	Treatment	18.28 (5.31)	17.98 (5.20)	−1.61	0.79	
Lean mass (kg)	Control	37.39 (7.36)	37.29 (7.16)	−0.26	0.52	0.2
	Treatment	40.25 (8.54)	40.35 (8.65)	0.23	0.54	

BMD (bone mineral density), BMC (bone mineral content)

were ensured by giving IM injections. Since we had a minimum drop outs the results are more robust.

Conclusions

This study showed that treatment with high dose vitamin D significantly influences total body BMC, total body BMD, BMDs of spine, femoral neck and hip among patients with diabetic nephropathy.

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Authors' contributions Dr. PLGC Liyanage conceived the idea, planned the study, collected patient information, analyzed and interpreted data drafted the paper and took part in revising and finalising the manuscript. Prof S Lekamwasam contributed for designing the study, supervised the study, analysed and interpreted data, edited the manuscript and approved the final version. Prof C Liyanage and Prof TP Weeraratne contributed for designing the study, supervised the study, edited the manuscript and approved final version. All authors are in agreement with the content of the manuscript.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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