Health-Related Quality of Life In T1DM Patients After High-Dose Cholecalciferol Supplementation.

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Research

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Abstract

Background: Type 1 Diabetes Mellitus (T1DM) impacts health-related quality of life (HRQoL). Cross-sectional studies suggest that low levels of vitamin D (VD) may impair HRQoL, however, the effect of VD supplementation on quality of life in patients with T1DM has not yet been clarified. The objective of the study was to evaluate the effects of high-dose VD supplementation on HRQoL in patients with T1DM.

Methods: We performed a prospective interventional study with 64 patients supplemented with high doses of cholecalciferol (4,000 IU/day for patients with 25-OH-vitamin D [25(OH)D] between 30 and 60 ng/mL, and 10,000 IU/day for those with 25(OH)D below 30 ng/mL) for 12 weeks. HRQoL was assessed with EuroQol instruments (EQ-5D and EQ-VAS).

Results: There was an improvement in global EQ-5D index at the end of vitamin D supplementation. Analysing only the EQ-5D domains, we observed particularly an improvement in mobility (1.3 ± 0.6 versus 1.1 ± 0.3 , $p < 0.01$). Evaluating possible outcome influencing variables, we detected a reduction in albuminuria at the end of the trial, without changes in BMI, lipids, blood pressure, glycemic control, insulin doses and in peripheral diabetic neuropathy. We also found a correlation between final albuminuria and the dimensions: mobility ($r = 0.6$; $p < 0.01$), personal care ($r = 0.7$; $p < 0.01$), pain and discomfort ($r = 0.6$; $p < 0.01$) and habitual activities ($r = 0.6$; $p < 0.01$), suggesting an association between albuminuria reduction and the impact of VD supplementation on HRQoL.

Conclusion: Our data showed that high doses of cholecalciferol supplementation can improve HRQoL in patients with T1DM, and the reduction of albuminuria seems to be an important factor in this context.

Trial registration: ISRCTN, ISRCTN32601947. Registered 3 June 2017 - Retrospectively registered, <http://www.isrctn.com/ISRCTN32601947>

Background

Type 1 diabetes mellitus (T1DM) is the most common endocrinopathy of childhood and adolescence and it is characterized by severe insulin deficiency, corresponding to approximately 10% of all diabetes cases, involving approximately 10 to 20 million individuals worldwide (1). Due to its high complexity, it is a disease with important physical, psychological and social repercussions and a considerable impact on the quality of life (QoL) of patients and their families (2)

The Brazilian Type 1 Diabetes Study Group (BrazDiab1SG) evaluating over 3,000 patients with T1DM, collected information from demographic, economic, clinical-laboratory and health-related quality of life (HRQoL), which was measured using EuroQol (3). Those data showed that variables as HbA1c, age, socioeconomic status (SES), physical activity, and the presence of micro and macrovascular complications were weakly associated with QoL, suggesting the need to investigate other factors that may affect this scenario (3).

Therefore, the association between hypovitaminosis D and HRQoL in patients with Diabetes Mellitus (DM), especially in T1DM, is still not well established (4, 5), considering that there are few clinical trials evaluating that, especially in the Southern Hemisphere. Thus, the aim of our study was to evaluate the effect of high-dose cholecalciferol supplementation on HRQoL of patients with T1DM.

Methods

A) Study design and patients

We performed a prospective study in order to evaluate the effect of high dose vitamin D supplementation in health-related quality of life (HRQoL) in patients with T1DM as part of a research protocol (ISRCTN32601947) that has already provided evidence on other aspects of VD supplementation outcomes (6–9). This trial was reviewed and approved by University Hospital João de Barros Barreto (HUJBB) ethics committee.

A total of 64 subjects were recruited from the endocrinology ambulatory department from HUJBB, signed consent was obtained from all patients. Participants were divided in two groups: patients with basal VD levels between 30 e 60 ng/mL (who received 4.000 IU /day of cholecalciferol) and patients with basal VD levels below 30 ng/mL (supplemented with 10.000 IU), both for 12 weeks.

Inclusion criteria consisted in: a) patient with T1DM diagnosis aged between 12 and 50 years, in at least a 1-year follow-up and in regular treatment with an endocrinologist; b) glycated hemoglobin $\geq 7\%$; c) insulin dose stability for at least 3 months before participating in the study; e) NPH, Glargine, Detemir, Aspart, Glulisin, Lispro, and Regular insulin were allowed; f) patients in use of metformin could participate of the study as long as they were using the same dose for at least 3 months; g) patients with hypertension and/or diabetic kidney disease (DKD) must be in stable doses of antihypertensive medication for at least four weeks; h) compliance with diet and exercise regimen. Exclusion criteria were: a) history of hepatic or bone metabolism disorders; b) previous VD or Calcium supplementation; c) abnormal serum creatinine levels d) anemias; e) breastfeeding and pregnant women; f) uncontrolled hypo or hyperthyroidism and allergies to VD supplementation; g) hemotransfusion and/or blood donation within the 3 months before the first visit. Patients were previously instructed to maintain physical activity regularly according to American Diabetes Association Guidelines (10) to avoid variations during the study.

B) Data collection

Data collection occurred during scheduled visits, during pre-treatment (baseline) and post-treatment (end of study) phases. Analysis of medical records (demographics, pre-existent clinical conditions, insulin and other medications in use) and physical examination were carried out. Laboratory tests and health-related quality of life evaluation (EQ-5D-5L and EQ- VAS) (11) were performed before and after twelve weeks.

Serum 25(OH)D was measured by DiaSorin LIAISON 25-OH-Vitamin D TOTAL chemiluminescence immunoassay (DiaSorin, Stillwater, MN, USA) (12) and immunoassay (13); HbA1C was analyzed by HPLC method. Fasting glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by colorimetry. The ultra-sensitive C-reactive protein was evaluated by ARCHITECT turbidimetry, and creatinine by the kinetic/automated method. The GFR was calculated by the CKD-EPI formula (10). Albuminuria was measured in three 24 h urine samples by immunoturbidimetry (14). Peripheral neuropathy was evaluated by two scores: Total Symptoms Score (TSS) and Neuropathy Disability Score (NDS). Presence of this complication was established by TSS $\geq$ 2 and NDS $\geq$ 3 (15, 16).

C) Quality of life assessment

Quality of life was assessed by the EuroQol 5 and its two tools: the EQ-5D-5L and EQ-VAS (11). The first one descriptively analyzes five dimensions of problems: mobility, self-care, pain and discomfort, usual activities, and anxiety and depression. Each dimension has five levels from "no problems" to "extreme problems". The EQ-VAS consists of an analog scale from 0 (poor health status) to 100 (optimal health status) for the patient to mark/say a value that reflects, in his/her perception, his/her health status. The HRQoL assessment tool was applied at basal and final visits.

The health states defined by the EQ-5D-5L responses were translated into EQ-5D utility index by means of sets of values that were derived from large population-based surveys. The utility index scale ranges from 0.0 to 1.0, where 0.0 represents death and 1.0 represents full health. As we did not have a publicly available set of EQ-5D-5L values for Brazilian population, in our study we used the set of values from the following countries: United States, Spain, Zimbabwe, Denmark, France, Germany, Japan, Netherlands, Thailand, and United Kingdom using the link (<https://euroqol.org/eq-5dinstruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/>).

D) Statistical analysis

Before and after VD supplementation, categorical variables were compared by Chi-square, Fisher and McNemar tests, while numerical ones were analysed with Student's T and Mann-Whitney tests, with and without normal distribution, respectively. Also, Paired Student's T and Wilcoxon tests were used to compare paired groups before and after the follow-up period, with normal and non-normal distribution, respectively. Data with normal distribution were represented as mean and standard deviation values, while data with non-normal distribution were represented by median and quartiles. To compare more than two groups, the analysis of variance test (ANOVA) was applied for normal distribution variables and Kruskal-Wallis test for abnormal distribution ones. Additionally, albuminuria values were converted to log base 10 (log₁₀) to better analyze the data. The level of statistical significance was set at $p < 0.05$ and all analyses were stored and processed with the software SigmaStat (Jandel Scientific) version 3.5 and SPSS (Statistical Package for Social Sciences) 22.0 IBM).

Results

Clinical characteristics at the beginning of the study are presented in Table 1.

Table 1
Clinical characteristics at the beginning of the study.

Clinical characteristics	N = 64
Age (Years)	27.6 ± 10.1
Gender (F/M)	33/31
DM duration (Years)	12.1 ± 8.1
History of dyslipidemia (Yes %)	15 (23.4%)
History of hypertension (Yes %)	10 (15.6%)
History of DKD (Yes %)	20 (31.2%)
History of Diabetic Retinopathy (Yes %)	11 (17.1%)
Smoking (Yes %)	10 (15.6%)
Previous treatment with ACEI/ARB (Yes %)	18 (28.1%)
T1DM: Type 1 Diabetes Mellitus; DKD: Diabetes Kidney Disease; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; F: female; M: male.	

Most patients of our sample (72%) had 25(OH)D levels below 30ng/ml, and, by the end of the trial, 94% of T1DM patients were classified with normal VD ($\geq 30\text{ng/ml}$) ($p < 0.001$).

In Table 2 are described the main clinical and laboratorial parameters before and after VD supplementation. By the end of the study, most analyzed parameters have not changed, except for 25(OH)VD levels (26.7 ± 9 versus $55.1 \pm 24.1 \text{ ng/mL}$, $p < 0.001$).

Table 2

Clinical and laboratory parameters of patients with T1DM before and after vitamin D supplementation.

Parameters (N = 64)	Pre VD	Post VD	P
BMI (kg/m ²)	24 ± 4	24 ± 4.	NS (0.247)
Systolic Blood Pressure (mmHg)	115 ± 11	115 ± 12	NS (0.765)
Diastolic Blood Pressure (mmHg)	71 ± 9	72 ± 9	NS (0.153)
Basal insulin dose (IU)	35.6 ± 17	36 ± 18	NS (0.957)
Prandial insulin dose (IU)	22.3 ± 12	23.3 ± 12	NS (0.177)
Total insulin dose (IU)	55.8 ± 27	58.1 ± 27	NS (0.708)
25(OH)VD (ng/mL)	26.7 ± 9	55.1 ± 24	< 0.001
HbA1c (%)	9.6 ± 2	9.8 ± 3	NS (0.250)
Fasting plasma glucose (mg/dL)	168 ± 96	180.6 ± 103	NS (0.497)
Ultrasensible CRP (mg/L)	0.36 ± 0.52	0.37 ± 0.54	NS (0.727)
Total cholesterol (mg/dL)	171.7 ± 41	177 ± 54	NS (0.292)
HDL cholesterol (mg/dL)	52 ± 38	44.6 ± 11	NS (0.293)
LDL cholesterol (mg/dL)	103.7 ± 31	107.9 ± 49	NS (0.714)
Non-HDL cholesterol (mg/dL)	123.5 ± 38	125.7 ± 50	NS (0.289)
Triglycerides (mg/dL)	97.7 ± 51	109.6 ± 70	NS (0.186)
IU = International Units; NS = Non significant; BMI = Body-Mass index; HbA1c = glycated hemoglobin; CRP: C-reactive protein; GFR = glomerular filtration rate; HDL = High-density lipoprotein; LDL = Low-density lipoprotein.			

On HRQoL evaluation by *EuroQol*, we found an improvement on EQ-5D-5L by the end of the study, according to electronic calculators available from evaluated countries, independently of Human Development Index (HDI) (Table 3).

Table 3
Utility index of EQ-5D before and after VD supplementation using a set of values of available countries.

Country	HDI	EQ-5D index before VD	EQ-5D index after VD	P
USA	0.926	0.87 ± 0.1	0.90 ± 0.1	< 0.05
Spain	0.904	0.88 ± 0.1	0.91 ± 0.1	< 0.05
Zimbabwe	0.571	0.83 ± 0.1	0.85 ± 0.1	< 0.05
Denmark	0.940	0.86 ± 0.1	0.89 ± 0.1	< 0.05
France	0.901	0.84 ± 0.2	0.89 ± 0.2	< 0.05
Germany	0.947	0.92 ± 0.1	0.94 ± 0.1	< 0.05
Japan	0.919	0.83 ± 0.1	0.87 ± 0.1	< 0.05
Thailand	0.777	0.79 ± 0.2	0.85 ± 0.2	< 0.01
UK	0.932	0.84 ± 0.2	0.88 ± 0.2	< 0.05
HDI: Human Development Index. UK: United Kingdo				

In EQ-5D, we observed an important improvement in mobility (1.3 ± 0.6 versus 1.1 ± 0.3 , $p < 0.01$) and there was also a tendency to improve in self-care dimension at the end of VD supplementation. We did not find additional changes in the other EQ-5D dimensions, as in the attributed grade to general health status, evaluated by EQ-VAS (Table 4).

Table 4
Analysis of EuroQol dimensions and grade of EQ-VAS before and after VD supplementation.

EQ-5D-5L dimensions	Before VD	After VD	p
1. Mobility	1.3 ± 0.6	1.1 ± 0.3	< 0.01
2. Self-care	1.1 ± 0.4	1.0 ± 0.3	0.125
3. Usual activities	1.3 ± 0.6	1.5 ± 0.7	0.669
4. Pain and discomfort	1.6 ± 0.8	1.5 ± 0.7	0.261
5. Anxiety and Depression	1.4 ± 0.7	1.4 ± 0.8	0.847
EQ-VAS	Before VD	After VD	P
Referred value	81 ± 17	80 ± 20	0.913

Main DM chronic complications before and after VD administration are shown on Table 5. We observed significant reduction in albuminuria (1.27 ± 0.7 versus 1.22 ± 0.7 , $p = 0.01$), with no changes in the other parameters.

Table 5
Clinical and laboratorial data concerning chronic T1DM complications
before and after VD supplementation.

Parameters (N = 64)	Pre VD	Post VD	P
Periferic neuropathy (Yes %)	25%	17%	NS (0.131)
PN – TSS	1.8 ± 2.3	1.6 ± 2.5	NS (0.166)
PN – NDS	2.1 ± 2.5	1.8 ± 2.6	NS (0.262)
Albuminuria (mg/24 h – Log10)	1.27 ± 0.7	1.22 ± 0.7	0.01
GFR (ml/min/1.73m2)	120 ± 37	117 ± 36	NS (0.247)

NS = Non significant; GFR = Glomerular Filtration Rate; HDL = High-density lipoprotein. LDL = Low Density lipoprotein; PN = peripheral neuropathy; TSS = Total Symptoms Score - Neuropathy; NDS = Neuropathy Disability Score.

Additionally, it was observed that final 25(OH)D levels showed correlation with final albuminuria ($r = -0.3$, $p < 0.05$) (Fig. 1). Therefore, the higher the 25(OH)D levels, the lower the albuminuria excretion rates by the end of VD supplementation.

In a post-hoc analysis, we compared patients who improved (group 1A, N = 51) or not (group 1B, N = 10) the EQ-5D utility index. We found an albuminuria reduction at the end of VD administration only in group 1A. No other differences were identified, except for increase in non-HDL and LDL cholesterol levels in group 1B at the end of the study (Table 6).

Furthermore, we performed a post-hoc analysis on patients with improvement (group 2A, n = 25) or not EQ-VAS (group 2B, n = 39), and found a significant increase in the dose of prandial insulin in group 2B (22.1 ± 13.1 UI versus 24.4 ± 12 UI, $p < 0.05$). Albuminuria reduced significantly only in group 2A (1.2 ± 0.7 versus 0.98 ± 0.7 ; $p < 0.05$). Besides that, we found that final albuminuria excretion was significantly lower in group 2A when compared to group 2B.

Table 6

Analysis of clinical and laboratorial parameters according to improvement (group 1A) or not (group 1B) of the EQ-5D utility index after VD supplementation.

	Group 1A (N = 51)		Group 1B (N = 10)		
Parameters	Pre VD	Post VD	Pre VD	Post VD	p
BMI (kg/m ²)	24 ± 4	24 ± 4	22 ± 3	22 ± 2	NS
Periferic neuropathy yes/no (%)	(13/51)	(8/51)	(1/10)	(1/10)	NS
	25%	16%	10%	10%	
Basal insulin dose (IU)	36 ± 18	37 ± 19	33 ± 18	30 ± 14	NS
Prandial insulin dose (IU)	23 ± 11	24 ± 11	20 ± 13	21 ± 12	NS
25(OH)VD (ng/mL)	27 ± 9	57 ± 25	26 ± 8	52 ± 23	< 0.001 ^{□□}
HbA1c (%)	9.5 ± 2.4	9.6 ± 2.5	10.1 ± 2.4	10.6 ± 3.6	NS
HDL cholesterol (mg/dL)	47 ± 12	45 ± 10	50 ± 11	49 ± 13	NS
LDL cholesterol (mg/dL)	105 ± 33	105 ± 51	97 ± 19	122 ± 35	< 0.005 ^{□*}
Non-HDL cholesterol (mg/dL)	123 ± 41	122 ± 52	117 ± 23	147 ± 45	0.01 [□]
Triglycerides (mg/ dL)	97 ± 53	108 ± 75	101 ± 43	111 ± 53	NS
Albuminuria (mg/24h – Log10)	1.25 ± 0.75	1.2 ± 0.75	1.27 ± 0.68	1.24 ± 0.54	< 0.05 [□]
□ : group 1A differs before and after VD					
□ : group 1B differs before and after VD					
* : group 1A differs from group 1B after VD					
NS = Non significant; BMI = Body-Mass Index; HbA1c = glycated hemoglobin; CRP = C-Reactive Protein; GFR = Glomerular Filtration Rate; HDL = High-density lipoprotein. LDL = Low-density lipoprotein					

Table 7

Analysis of clinical and laboratorial parameters according to improvement (Group 2A) or not (Group 2B) of EQ-VAS at the end of vitamin D supplementation.

	Group 2A (N = 25)		Group 2B (N = 39)		
Parameters	Pre VD	Post VD	Pre VD	Post VD	p
BMI (kg/m ²)	23.3 ± 4	23.4 ± 4	24.3 ± 5	24.3 ± 5	NS
Periferic neuropathy yes/no (%)	(4/21) 16%	(3/22) 12%	(12/27) 30%	(8/31) 21%	NS
Basal insulin dose (IU)	36 ± 14.2	39 ± 19	35 ± 19	34 ± 19	NS
Prandial insulin dose (IU)	22.7 ± 9	21.7 ± 10	22.1 ± 13	24.4 ± 12	< 0.05 [□]
25(OH)VD (ng/mL)	26.1 ± 9	62.7 ± 27	27.1 ± 9	50.3 ± 20	< 0.001 ^{□□}
HbA1c (%)	9.6 ± 2	9.7 ± 3	9.6 ± 2	9.8 ± 3	NS
HDL cholesterol (mg/dL)	47 ± 10	44 ± 8	48 ± 13	46 ± 12	NS
LDL cholesterol (mg/dL)	126 ± 27	122 ± 30	122 ± 43	128 ± 58	NS
Non-HDL cholesterol (mg/dL)	88 ± 28	96 ± 46	107 ± 60	118 ± 83	NS
Albuminúria (mg/24h – Log10)	1.2 ± 0.7	0.98 ± 0.7	1.3 ± 0.8	1.4 ± 0.7	< 0.05 ^{□*}
□ Group 2B differs before and after VD					
□ Group 2A differs before and after VD					
* Group 2A differs from Group 2B after VD					
NS = Non significant; BMI = Body-Mass Index; HbA1c = glycated hemoglobin; CRP = C-Reactive Protein; GFR = Glomerular Filtration Rate; HDL = High-density lipoprotein. LDL = Low-density lipoprotein					

On patients with an improvement of EQ-VAS at the end of the study (Group 1A), we also observed a correlation between final albuminuria and the following dimensions of EQ-5D: mobility ($r = 0.6$; $p < 0.01$), self-care ($r = 0.7$; $p < 0.01$), habitual activities ($r = 0.6$; $p < 0.01$) and pain and discomfort ($r = 0.6$; $p < 0.01$).

Discussion

Our findings suggested an improvement in T1DM patients quality of life (QoL) after supplementation with high doses of cholecalciferol. According to our knowledge, this is the first clinical trial to demonstrate the impact of VD supplementation on HRQoL in this population.

Few studies addressing VD supplementation on HRQoL in patients with diabetes have been conducted. Krul-Poel et al. performed a randomized, double-blind, placebo-controlled trial with 275 patients with type

2 diabetes mellitus (T2DM), who monthly supplemented 50,000 IU of cholecalciferol during six months, and found no changes in QoL at the end of the study. Similarly, Mager et al. analyzed the impact of administering different doses of vitamin D3 (2000 IU day or 40,000 IU monthly) for six months in T2DM patients with chronic kidney disease (CKD), and did not detect improvement in their HRQoL. Those results differ from ours since the patients in the present trial received higher doses of cholecalciferol. Furthermore, both studies used cholecalciferol monthly, in contrast to cholecalciferol daily doses in our trial which have a different biological effect (17–19).

Additionally, the improvement of HRQoL in our study was found by analysis of EQ-5D-5L index after supplementation of cholecalciferol for 12 weeks. We noticed a change in the final EQ-5D-5L index using sets of values from all countries available. It was important to unify the 5 dimensions of problems in a single index to obtain our results. It is our knowledge that additional studies are necessary to establish the importance of each dimension for the Brazilian population. For that, are required both a traditional method validation, performed in Brazil in 2015, and a populational study, which has not happened in this country yet (20). However, our findings showed improvement of EQ-5D-5L index using sets of values from countries of different continents, with different populations and the most diverse HDIs, which gives a lot of consistency to our results.

When we analysed each dimension of EQ-5D in this trial, we found an improvement of mobility. Moreover, self-care dimension showed a tendency to be better by the end of VD administration. Those results differ from Raymakers et al, who describe, in a cross-sectional study, a greater impact of anxiety/depression dimension in HRQoL, evaluating 473 patients with T1DM in Ireland. Nonetheless, it is important to notice that in BrazDiab1SG, as described by Felício et al., patients in North and Northeast regions reported lower frequency of anxiety and depression when compared to other Brazilian regions. (3, 21). In addition, it is known that geographic aspects, especially temperature and sun exposure, can affect quality of life (22). The consistent improvement of EQ-5D-5L index when evaluated by sets of values from countries that represent almost all geographical regions validates our findings.

It is well known that skeletal muscle fibers carry VD receptors, and their activation is a possible mechanism of muscle growth (17, 23). Biopsy and consistent findings of muscle atrophy were associated with VD deficiency (24). Moreover, Sato et al. (2005) showed that calcium and vitamin D supplementation improves muscle fibers in number and size, as well as the lower members function. Randomized controlled trials and meta-analyses have shown that 25(OH)D supplementation decreases risk of falls and fractures in elderly patients (24–27). Finally, VD deficiency is associated with muscle atrophy, musculoskeletal pain and worse physical function in the general population (28). In our sample, most patients had hypovitaminosis D (VD < 30ng/ml) at the beginning of the study and, by the end of the supplementation, 94% of them had sufficient levels of 25 (OH) D. It could have potentiated extra-skeletal actions of VD (29). Thus, the hypothesis that VD affected mobility and QoL in our study by its direct action on muscle fibers must be considered.

Our results also demonstrated a reduction in albumin excretion at the end of cholecalciferol supplementation. It particularly occurred in the subgroups that improved QoL in post-hoc analysis. In addition, there was a correlation between final 25(OH)D levels and final albuminuria. Felício et al. in a pilot study that analyzed patients with T1DM who received 4,000 and 10,000 units of cholecalciferol for 12 weeks according to their previous 25(OH)D levels found a reduction in prevalence of diabetic kidney disease (DKD) and a correlation between the percentage of VD levels variation and albuminuria after cholecalciferol supplementation (7). There is growing evidence that vitamin D given in high doses can be renoprotective (30, 31). Humalda et al. (2015) performed a systematic review of all randomized clinical trials with calcitriol or paricalcitol as an antiproteinuric intervention. During follow-up, VD active analogs reduced proteinuria by an average of 16%. These results were obtained, in most cases (84%), in patients under chronic treatment of previous conditions with renin angiotensin aldosterone inhibitors, accentuating the capacity of VD analogs to reduce residual proteinuria. Those authors suggest that compensatory increase in renin is a paradoxical event secondary to the use of SARS inhibitors, and can be antagonized by calcitriol (32). Furthermore, Wolfgram et al. (2017) presented a secondary analysis of the cross-sectional study SPRINT (Systolic Blood Pressure Intervention Trial), in which they evaluated a subgroup of individuals with age greater than 75 years. In addition to renal indexes (GFR and albuminuria), participants in this subgroup underwent gait speed assessment, self-assessment of HRQoL with a focus on functional status (EQ-5D), and assessment risk of falling. In the unadjusted model, the decrease in eGFR and increase in categories of albuminuria were associated with worse scores in the three tools. This data raises the hypothesis that VD may also contribute to an improvement in quality of life through its positive effect in DRD (33).

Studies have shown that, among patients with CKD, HRQoL gradually declines as the disease progresses, with the worst HRQoL scores obtained when an advanced stage of kidney disease is reached (34, 35). When CKD coexists with diabetes an accentuated deterioration in HRQoL is expected (36). However, few studies have examined this relationship in the early stages of CKD or attempted to incorporate albuminuria in this assessment. According to Bowling et al., albuminuria may be more sensitive than glomerular filtration rate (GFR) to identify patients with risk of functional impairment, at least in early stages of CKD (37). In our study, abnormal creatinine levels were an exclusion criteria. Therefore, our data reinforce these findings.

The main limitations of our study were short duration (12 weeks) and absence of a placebo control group. Following this study, controlled, double-blind, randomized trials with a placebo group and a longer duration of supplementation should be performed to confirm our findings.

Conclusion

Our data demonstrated an improvement in HRQoL after supplementation of high doses of cholecalciferol in patients with T1DM. There was an improvement in the EuroQoL utility index (EQ-5D-5L), and in mobility dimension. Additionally, the reduction of albuminuria seems to be an important factor in this context.

Abbreviations

ANOVA: Analysis of Variance Test

CKD: Chronic Kidney Disease

DKD: Diabetic Kidney Disease

DM: Diabetes Mellitus

GFR: Glomerular Filtration Rate

HDI: Human Development Index

HDL-C: High-density Lipoprotein Cholesterol

HRQoL: Health-related Quality of Life

HUJBB: University Hospital João de Barros Barreto

LDL-C: Low-density Lipoprotein Cholesterol

NDS: Neuropathy Disability Score

SES: Socioeconomic Status

TSS: Total Symptoms Score

T1DM: Type 1 Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

QoL: Quality of Life

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Our study was approved by the Human Research Ethics Committee. The Committee waived the requirement for written informed consent for participants in this study in accordance with the national legislation, resolution 466/12 (National Health Council) and the institutional requirements due to the fact that it is a database population study with confidentiality and non-identification guarantee.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTEREST

The authors declare that they have no competing interests

FUNDING

The authors received no specific funding for this work.

AUTHORS' CONTRIBUTIONS

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. ACCBS, MCNIO, GNL, ALA, ERS, took part in conception and design of study. NMS, SRP, AAAM, LVM were responsible for acquisition of data, while WMS, IJAS, and JFAN have done the analysis and interpretation of data. NNMQ, FTM, KMF, LSDS, SLG, NAM, PPFP, IJCL, JSF have drafted the manuscript together. All authors have revised the manuscript critically and approved the version to be published.

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References

1. International Diabetes Federation. IDF Diabetes Atlas Ninth. Dunia: IDF; 2019.
2. Felício JS, Silva LSAA, Santos FM. Qualidade de vida do paciente com Diabetes Mellitus tipo 1. Diabetes 1 no Brasil. 1st ed. São Paulo: CLANNAD; 2019.
3. On behalf of the Brazilian Type 1 Diabetes Study Group (BrazDiab1SG), Braga. de Souza ACC, Felício JS, Koury CC, Neto JFA, Miléo KB, et al. Health-related quality of life in people with type 1 Diabetes Mellitus: data from the Brazilian Type 1 Diabetes Study Group. Health Qual Life Outcomes. dezembro de 2015;13(1):204.
4. Alcubierre N, Castelblanco E, Martínez-Alonso M, Granado-Casas M, Esquerda A, Traveset A, et al. Vitamin D deficiency is associated with poorer satisfaction with diabetes-related treatment and quality of life in patients with type 2 diabetes: a cross-sectional study. Health Qual Life Outcomes. 2018;16:44. <https://doi.org/10.1186/s12955-018-0873-3>.

5. Anand S, Kaysen GA, Chertow GM, Johansen KL, Grimes B, Dalrymple LS, et al. Vitamin D deficiency, self-reported physical activity and health-related quality of life: the Comprehensive Dialysis Study. *Nephrology Dialysis Transplantation*. 2011;26:3683–8. <https://doi.org/10.1093/ndt/gfr098>.
6. de Queiroz NNM, de Melo FTC, de Souza Resende F, Janaú LC, de Souza Neto NJK, de Lemos MN, et al. High-dose Cholecalciferol Supplementation Reducing Morning Blood Pressure in Normotensive DM1 Patients. *CDR*. 2021;17:378–86. <https://doi.org/10.2174/1573399816999200729131508>.
7. Felício JS, Oliveira AF de, Peixoto AS, Souza ACCB de, Abrahão Neto JF, de Melo FTC, et al. Albuminuria Reduction after High Dose of Vitamin D in Patients with Type 1 Diabetes Mellitus: A Pilot Study. *Front Endocrinol*. 2017;8:199. <https://doi.org/10.3389/fendo.2017.00199>.
8. Felício JS, Luz RM, de Melo FTC, de Souza Resende F, de Oliveira AF, Peixoto AS, et al. Vitamin D on Early Stages of Diabetic Kidney Disease: A Cross-sectional Study in Patients with Type 1 Diabetes Mellitus. *Front Endocrinol* 2016;7. <https://doi.org/10.3389/fendo.2016.00149>.
9. Felício KM, de Souza ACCB, Neto JFA, de Melo FTC, Carvalho CT, Arbage TP, et al. Glycemic Variability and Insulin Needs in Patients with Type 1 Diabetes Mellitus Supplemented with Vitamin D: A Pilot Study Using Continuous Glucose Monitoring System. *CDR* 2018;14:395–403. <https://doi.org/10.2174/1573399813666170616075013>.
10. Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, Feldman HI et al A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009;150:604. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006>.
11. Balestroni G, Bertolotti G. EuroQol-5D (EQ-5D): an instrument for measuring quality of life. *Monaldi Arch Chest Dis* 2015;78. <https://doi.org/10.4081/monaldi.2012.121>.
12. DiaSorin. LIAISON 25 OH vitamin D TOTAL Assay [Brochure]. [Internet]. Available from: <https://www.diasorin.com/en/node/8476>.
13. Wagner D, Hanwell HEC, Vieth R. An evaluation of automated methods for measurement of serum 25-hydroxyvitamin D. *Clin Biochem*. 2009;42:1549–56. <https://doi.org/10.1016/j.clinbiochem.2009.07.013>.
14. Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? *Diabetes Metabolism*. 2008;34:612–6. <https://doi.org/10.1016/j.diabet.2008.04.005>.
15. Young MJ, Boulton AJM, Macleod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia*. 1993;36:150–4. <https://doi.org/10.1007/BF00400697>.
16. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care*. 1999;22:1296–301. <https://doi.org/10.2337/diacare.22.8.1296>.

17. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a Short-Term Vitamin D3 and Calcium Supplementation on Blood Pressure and Parathyroid Hormone Levels in Elderly Women¹. *The Journal of Clinical Endocrinology Metabolism*. 2001;86:1633–7. <https://doi.org/10.1210/jcem.86.4.7393>.
18. Krul-Poel YHM, Westra S, van Wijland HJJ, Stam F, Lips P, Pouwer F, et al. Vitamin D status and health-related quality of life in patients with Type 2 diabetes. *Diabet Med*. 2016;33:300–6. <https://doi.org/10.1111/dme.12834>.
19. Mager DR, Jackson ST, Hoffmann MR, Jindal K, Senior PA. Vitamin D 3 supplementation, bone health and quality of life in adults with diabetes and chronic kidney disease: Results of an open label randomized clinical trial. *Clin Nutr*. 2017;36:686–96. <https://doi.org/10.1016/j.clnu.2016.05.012>.
20. Santos M, Cintra MACT, Monteiro AL, Santos B, Gusmão-filho F, Andrade MV, et al. Brazilian Valuation of EQ-5D-3L Health States: Results from a Saturation Study. *Med Decis Making*. 2016;36:253–63. <https://doi.org/10.1177/0272989X15613521>.
21. Raymakers AJN, Gillespie P, O'Hara MC, Griffin MD, Dinneen SF. Factors influencing health-related quality of life in patients with Type 1 diabetes. *Health Qual Life Outcomes*. 2018;16:27. <https://doi.org/10.1186/s12955-018-0848-4>.
22. McCue M, Fairman A, Pramuka M. Enhancing Quality of Life through Telerehabilitation. *Physical Medicine Rehabilitation Clinics of North America*. 2010;21:195–205. <https://doi.org/10.1016/j.pmr.2009.07.005>.
23. Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ, et al. Addressing the Musculoskeletal Components of Fracture Risk with Calcium and Vitamin D: A Review of the Evidence. *Calcif Tissue Int*. 2006;78:257–70. <https://doi.org/10.1007/s00223-005-0009-8>.
24. Bischoff HA, Helin HBS, Dick W, Akos R, Knecht M, Salis C, et al. Effects of Vitamin D and Calcium Supplementation on Falls: A Randomized Controlled Trial.:9.
25. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, et al. Should Older People in Residential Care Receive Vitamin D to Prevent Falls? Results of a Randomized Trial: VITAMIN D TREATMENT TO PREVENT FALLS. *J Am Geriatr Soc*. 2005;53:1881–8. <https://doi.org/10.1111/j.1532-5415.2005.00468.x>.
26. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A Higher Dose of Vitamin D Reduces the Risk of Falls in Nursing Home Residents: A Randomized, Multiple-Dose Study: VITAMIN D AND FALLS IN NURSING HOME RCT. *J Am Geriatr Soc*. 2007;55:234–9. <https://doi.org/10.1111/j.1532-5415.2007.01048.x>.
27. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-Dose Vitamin D Prevents Muscular Atrophy and Reduces Falls and Hip Fractures in Women after Stroke: A Randomized Controlled Trial. *Cerebrovasc Dis*. 2005;20:187–92. <https://doi.org/10.1159/000087203>.
28. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, et al. Association Between Vitamin D Status and Physical Performance: The InCHIANTI Study. *The Journals of Gerontology*

- Series A: Biological Sciences Medical Sciences. 2007;62:440–6.
<https://doi.org/10.1093/gerona/62.4.440>.
29. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D. Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol Rev*. 2016;96:365–408.
<https://doi.org/10.1152/physrev.00014.2015>.
30. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *The Lancet*. 2010;376:1543–51.
[https://doi.org/10.1016/S0140-6736\(10\)61032-X](https://doi.org/10.1016/S0140-6736(10)61032-X).
31. Zhang Z, Sun L, Wang Y, Ning G, Minto AW, Kong J, et al. Renoprotective role of the vitamin D receptor in diabetic nephropathy. *Kidney Int*. 2008;73:163–71. <https://doi.org/10.1038/sj.ki.5002572>.
32. Humalda JK, Goldsmith DJA, Thadhani R, de Borst MH. Vitamin D analogues to target residual proteinuria: potential impact on cardiorenal outcomes. *Nephrol Dial Transplant*. 2015;30:1988–94.
<https://doi.org/10.1093/ndt/gfu404>.
33. Wolfgram DF, Garcia K, Evans G, Zamanian S, Tang R, Wiegmann T, et al. Association of Albuminuria and Estimated Glomerular Filtration Rate with Functional Performance Measures in Older Adults with Chronic Kidney Disease. *Am J Nephrol*. 2017;45:172–9. <https://doi.org/10.1159/000455388>.
34. Zimbudzi E, Lo C, Ranasinha S, Teede H, Usherwood T, Polkinghorne KR, et al. Health-related quality of life among patients with comorbid diabetes and kidney disease attending a codesigned integrated model of care: a longitudinal study. *BMJ Open Diab Res Care*. 2020;8:e000842.
<https://doi.org/10.1136/bmjdrc-2019-000842>.
35. Wyld MLR, Morton RL, Clayton P, Wong MG, Jardine M, Polkinghorne K, et al. The impact of progressive chronic kidney disease on health-related quality-of-life: a 12-year community cohort study. *Qual Life Res*. 2019;28:2081–90. <https://doi.org/10.1007/s11136-019-02173-1>.
36. Krishnan A, Teixeira-Pinto A, Lim WH, Howard K, Chapman JR, Castells A, et al. Health-Related Quality of Life in People Across the Spectrum of CKD. *Kidney International Reports*. 2020;5:2264–74.
<https://doi.org/10.1016/j.ekir.2020.09.028>.
37. Bowling CB, Bromfield SG, Colantonio LD, Gutiérrez OM, Shimbo D, Reynolds K, et al. Association of Reduced eGFR and Albuminuria with Serious Fall Injuries among Older Adults. *CJASN*. 2016;11:1236–43. <https://doi.org/10.2215/CJN.11111015>.

Figures

Figure 1

Correlation between albuminuria and 25(OH)D levels at the end of the study.