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Effects of 12 weeks high dose vitamin D3 treatment on insulin sensitivity, beta cell function, and metabolic markers in patients with type 2 diabetes and vitamin D insufficiency – a double-blind, randomized, placebo-controlled trial☆,☆☆

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ABSTRACT

Objectives. Vitamin D insufficiency is common in subjects with type 2 diabetes. Observational studies suggest that vitamin D plays a role in the pathogenesis of type 2 diabetes. However, results of intervention studies have been inconsistent. We investigated the effects of improving vitamin D status on insulin sensitivity, insulin secretion, and inflammatory markers in patients with type 2 diabetes.

Materials/methods. A double blind, randomized, placebo controlled trial was conducted. Sixteen patients with type 2 diabetes and hypovitaminosis D were recruited. Eight patients received colecalciferol and (280 μg daily for 2 weeks, 140 μg daily for 10 weeks) and 8 patients received identical placebo tablets for 12 weeks. Before and after intervention, patients underwent IVGTT, hyperinsulinemic euglycemic clamp, assessment of baseline high-frequency insulin pulsatility, glucose-entrained insulin pulsatility, DXA scans, 24-hour-ambulatory blood pressure monitorings, and fasting blood samples.

Results. Serum-25(OH) vitamin D and serum-1,25$(OH)_2$ vitamin D increased significantly after 12 weeks in the intervention group ($p = 0.01$, $p = 0.004$). Serum-25(OH) vitamin D was also significantly higher in the vitamin D group compared to the placebo group ($p = 0.02$) after intervention. Although no significant changes in insulin sensitivity, inflammation,

Abbreviations: 25OHD, 25-hydroxyvitamin D; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; HOMA, Homeostasis Model Assessment; IGT, impaired glucose tolerance; BMD, bone mineral density; GCP-Unit, Good Clinical Practice; ApEn, approximate entropy; IVGTT, intravenous glucose tolerance test; AUC, areas under the curve; PTH, parathyroid hormone; DXA, dual-energy X-ray absorptiometry; ABPM, ambulatory blood pressure monitoring; TCI, transient cerebral ischemia; OGIS, oral glucose insulin sensitivity.

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blood pressure, lipid profile, or HbA1c were found, we observed borderline (p between 0.05 and 0.10) improvements of insulin secretion, in terms of c-peptide levels, first phase incremental AUC insulin and insulin secretory burst mass.

Conclusions. Improvement in vitamin D status does not improve insulin resistance, blood pressure, inflammation or HbA1c, but might increase insulin secretion in patients with established type 2 diabetes.

1. Introduction

Vitamin D deficiency is a worldwide health problem and the finding that most organs and immune cells in the body have vitamin D receptors has provided new insights into the non-skeletal effects of vitamin D [1]. A relationship between lack of vitamin D and development of type 1 diabetes has been reported [2–4] and several observational studies suggest a role of vitamin D in the pathogenesis of type 2 diabetes. In the Nurse's Health Study low vitamin D intakes were associated with a higher risk of developing type 2 diabetes [5] and serum 25OHD concentrations were inversely related to the prevalence of diabetes in the Third National Health and Nutrition Examination Survey (1988–1994) [6] as well as to insulin resistance in a smaller cross sectional study [7]. In a 10-year prospective study an inverse association between baseline serum 25OHD and future glycemia and insulin resistance was found [8]. Despite supporting evidence from abundant observational studies the results of intervention studies with vitamin D on glucose metabolism and other components of the metabolic syndrome have been inconsistent [9–22]. The available trials are conducted in different settings with differences in subject populations, length of intervention and forms of vitamin D supplementation. In addition, most studies have used indirect measures of insulin secretion and sensitivity (HOMA) and are unable to show relevant increase in serum 25OHD [19,23]. Most studies regarding the potential effects of vitamin D on glucose metabolism have examined normal subjects or subjects with impaired glucose tolerance (IGT). Whether vitamin D has an impact on metabolic control and complications in patients with established diabetes has not been well addressed. It is however an area of great importance as many individuals with diabetes are vitamin D insufficient [6,23].

Also only limited and conflicting data exist concerning the relationship between vitamin D status and systemic inflammation in type 2 diabetes [5,12,24].

This study was designed to investigate the effects of improved vitamin D status on insulin sensitivity, insulin secretion, and on inflammatory markers in vitamin D insufficient patients with type 2 diabetes. As vitamin D status has been associated with plasma lipid concentrations, blood pressure [19,22,25], and bone mineral density (BMD) [26] these variables were also measured.

2. Methods

The study design was a randomized, placebo-controlled, double-blind trial. Danish participants aged ≥18 years with a diagnosis of type 2 diabetes mellitus were recruited from a primary care and a secondary care diabetes clinic. Exclusion criteria were as follows: Serum 25OHD level ≥50 nmol/L; serum urea >12 mmol/L; serum total calcium >2.52 mmol/L, a history of coronary infarction, sarcoidosis, malabsorption, primary hyperparathyroidism or malignancy. Women, who were pregnant, lactating or not undertaking effective contraceptive measures, were also excluded. In total 192 patients were screened (Fig. 1). Sixteen patients (8 men and 8 women) were enrolled for 12 weeks. Subjects were advised to contact research staff immediately if they suspected a reaction to the supplements and all adverse events were recorded. To avoid sun exposure and thus dermal production of vitamin D, the intervention period was from December until March. Participants were not allowed to use tanning beds or to travel at latitudes below 52°, where photoconversion of 7-dehydrocholesterol to previtamin D occurs during winter months, nor were they allowed to take vitamin D or calcium supplements during the intervention period, except from what was provided in the study. The study was conducted in accordance with the Helsinki Declaration and monitored by the GCP-Unit at Aarhus University Hospital. The study protocol was reviewed and approved by the Regional Ethical Committee and the Danish Medicines Agency and the nature and potential risks were explained before participants gave written informed consent. The protocol was registered at clinicaltrials.gov (ID: NCT00812578).

A summary of the study design is depicted in Fig. 1. Recruited subjects were randomized into a treatment group of eight (2 women, 6 men), who received oral cholecalciferol (11,200 IU (280 μg) daily for 2 weeks, followed by 5600 IU (140 μg) daily for 10 weeks) and eight patients (6 women, 2 men) who received placebo (tablets identical to the cholecalciferol tablets in number and external appearance). A restricted block randomization procedure was used. Four individuals were included in each block; two subjects were randomly allocated to placebo, two subjects received cholecalciferol. Neither data collectors nor the laboratory staff knew the randomized group status of the participants. The participants were asked to fill out a questionnaire at baseline concerning medical conditions, medication, vitamin D and calcium intake, sun exposure, smoking habits, and physical activity, and they were advised to continue their lifestyle during the intervention period. Moreover, they were instructed not to change dosages of their antihypertensive or antidiabetic medicine (insulin and/or metformin) during the trial.

Outcome measures were performed at baseline (immediately prior to first dosing) and after 12 weeks.