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Randomized control trials

Vitamin D_3 supplementation and body composition in persons with obesity and type 2 diabetes in the UAE: A randomized controlled double-blinded clinical trial☆

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SUMMARY

Background & aim: The co-existence of vitamin D deficiency with obesity and type 2 diabetes is highly prevalent in the United Arab Emirates. We do not have studies evaluating the vitamin D dose response and sufficiency, and if sufficient substitution dose during a longer period could decrease obesity or change fat distribution in obese type 2 diabetic vitamin D deficient Emiratis.

Methods: A randomized double-blind clinical trial was conducted for 6 months followed by another 6 months of un-blinded follow up with 87 obese, type 2 diabetic participants. Serum 25-hydroxy vitamin D (S-25(OH)D), anthropometric data, and life-style factors such as diet and sunlight exposure were measured. The study was executed in 3 phases in two arms vitamin D arm ($n = 45$) and placebo arm ($n = 42$); in Phase 1 the vitamin D arm received 6000 IU vitamin D_3/day (3 months) followed by Phase 2 with 3000 IU vitamin D_3/day. During follow up (phase 3) both the arms were un-blinded and supplemented with 2200 IU vitamin D_3/day for another 6 months.

Results: At the baseline a significant ($p < 0.01$) positive association between body fat mass and body weight ($r = 0.97$) muscle mass ($r = 0.47$), water mass ($r = 0.54$), waist circumference ($r = 0.82$) and serum PTH ($r = 0.28$) was observed. On supplementation no significant changes in anthropometric dimensions was observed. S-25(OH) D peaked in phase 1 (77.2 ± 30.1 vs 28.5 ± 9.2, $p = 0.003$) followed by a decrease in phase 2 (62.3 ± 20.8, $p = 0.006$) paralleled by a decrease in parathyroid hormone in phase 2 (5.9 ± 2.4 vs 4.5 ± 1.8, $p < 0.01$) compared to baseline in vitamin D group.

Conclusion: This study shows no significant influence of vitamin D supplementation on weight, fat mass or waist circumference in type 2 diabetic obese vitamin D deficient participants of Arab ethnicity after one year. Despite a relatively high daily dose of vitamin D_3 we did not achieve target levels of S-25(OH)D above 75 nmol/L in this population. However, supplementation was safe, improved s- 25 (OH)D also reducing the incidence of eucalcemic parathyroid hormone elevation.

Clinical trial registry: ClinicalTrials.gov Identifier: NCT02101151.

1. Introduction

The United Arab Emirates (UAE) has been bearing a dual burden of a rapid increase in obesity (37%) and type 2 diabetes (T2D) (19%) across all age groups [1,2]. This has been paralleled with the resurgence of vitamin D deficiency in the Arab region [3,4]. The role of vitamin D in skeletal health is undisputed, however recently it has been associated with chronic diseases like cardiovascular disease, diabetes mellitus and cancer [5]. Several authors have also indicated poor vitamin D status in obese adults, and linked it to

Abbreviations: 25(OH) D, 25 hydroxy-vitamin D; BMI, Body Mass Index; UAE, United Arab Emirates; T2D, Type 2 diabetes mellitus; PTH, Parathyroid Hormone; ALP, Alkaline phosphatase.

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sequestration of this fat soluble vitamin in adipose tissue and to the possibility that the obese adults are less likely to engage in outdoor activities, and so their exposure to direct sunlight is low. If vitamin D is to have a causal role, then changes in the vitamin D status could be related to changes in the weight status. However, the underlying explanations and direction of causality are unclear [6].

Obesity and vitamin D deficiency are suggested to be among the important modifiable risk factors for cardiovascular diseases and diabetes mellitus. Evidence shows that a modest weight loss may also provide clinical benefits in individuals with diabetes, especially those early in disease process [7]. Reports from cellular, animal and epidemiological studies in the last decade have hypothesized possible role of calcium and vitamin D in body weight regulation [8,9]. These effects of vitamin D may be mediated by the hormonally active metabolite 1, 25-dihydroxy vitamin D or via suppression of plasma levels of intact parathyroid hormone (PTH) [10]. However, evidence from randomized controlled trials on the effect of vitamin D supplementation in obese and/or diabetic participants have led to inconsistent results [11–13].

In our previous randomized controlled trial [14] we showed that 6 months intervention with vitamin D_3 did not improve glycemic control among obese type 2 diabetic participants. However, in the present study anthropometric data, life-style factors and serum 25-hydroxy vitamin D (S-25(OH) D) concentrations are described during this intervention followed by another 6 months intervention in both groups.

The main aim of the present study was to investigate if restoring vitamin D status by increasing serum levels of 25(OH) D would decrease obesity and change fat distribution. Secondly, we also wanted to investigate changes in S-25(OH)D levels and PTH during supplementation to characterize the dose–response of different doses of vitamin D_3 for one year.

As the studies on vitamin D supplementation and optimal vitamin D levels are controversial and results divergent, our study is one of the few clinical trials undertaken in this region to assess the effect of vitamin D_3 supplementation on body composition in vitamin D deficient obese T2D patients in the UAE. The outcome should be valuable to both clinical practice and public health for this region.

2. Methodology

2.1. Subjects

This randomized trial was done at Rashid Centre for Diabetes and Research, a tertiary outpatient diabetes care clinic in Ajman, UAE during June 2012 to June 2013. The patients included were male and female, age between 30 and 60 years, UAE national, body mass index (BMI) $\geq$30 kg/m^2, diagnosed with T2D and S-25(OH)D levels <50 nmol/L. Patients were excluded if possible primary hyperparathyroidism (P-PTH >5.0 pmol/L) combined with plasma calcium $\geq$2.8 mmol/L, liver function tests (alkaline phosphatase [ALP], alanine amino transferase, bilirubin) >3 times the upper limit of the local reference range, serum creatinine >200 μmol/l; malabsorption syndrome, on anticonvulsants, corticosteroids or vitamin D supplementation and pregnant or lactating.

Eighty seven patients acknowledged their participation in the trial by giving a written informed consent, which was approved by the Ethical committee of the Ministry of Health, UAE.

2.2. Study design

Participants selected based on inclusion-exclusion criteria were randomized by a computer-generated random number sequence into either vitamin D arm (D-group) (n = 45) or placebo arm (P-group) (n = 42) stratified by age, gender and BMI by the Rashid Centre for Diabetes and Research, Information and Technology department. Vitamin D_3 (Cholecalciferol) (Solgar, Leonia, New Jersey, USA) and placebo (Starch) (Compound Pharmacy, Dubai, UAE) capsules were identical, and dispensed as described elsewhere [14].

Figure 1 illustrates summary of the study design. The intervention period included phase 1 and phase 2 for three months each and follow up period in phase 3 for six months. In phase 1 the D-group received unlabeled oral 6000 IU vitamin D_3/day, while P-group received matching placebo capsules. During phase 2, D-group received 3000 IU Vitamin D3/day of and P-group continued with matching placebo. The design is described in detail elsewhere [14]. Compliance was assessed during the clinic visit at 3 and 6 months. The participants and research team remained blinded until the intervention period was completed. In Phase 3 (Follow up) the cohort was un-blinded and both groups continued on maintenance dose of 2200 IU vitamin D_3/day along with the regular medical care.

2.3. Measurements

All measurements were repeated at baseline, end of Phase 1, 2 and 3. Body weight and height was measured using an electronic balance with stadiometer (SECA-Germany) and recorded to the nearest 0.1 kg and 0.1 cm respectively. Body composition was assessed by bioelectric impedance using InBody-230 (Biospace, Dogok-dong, South Korea) under standardized conditions i.e., 2 h fasting, no intense physical exercise 12 h prior to the test, no menstruation $\pm$ 2 days. Body mass index (weight (kg)/height^2 (m^2)) was also estimated. Waist circumference (WC) was defined as the abdominal circumference immediately above the iliac crest.

A pretested standard questionnaire was answered by the participants to record baseline information on intake of food sources rich in cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Additional information on outdoor exposure to sunlight, clothing, use of sunscreens and skin color (Fitzpatrick scale) is described elsewhere [14]. Fasting (12 h) venous blood samples (8 ml) was collected for the measurement of plasma calcium, PTH and phosphorous using Enzymatic IFCC-IDMS Standardized in Roche COBAS 6000 analyzer (Mannheim, Germany). S-25(OH)D was measured with a chemiluminescence method, Liason 25(OH) vitamin D TOTAL, performed in Diasorin Liaison analyzer (Saluggia, Italy). The assay depends on an antibody that can detect both 25-OH-D2 and 25-OH-D3 and the company DiaSorin claim 100% cross-reactivity on an equimolar basis. The analyzing laboratory participated in the vitamin D external quality assessment scheme (DEQAS). All variables were measured at the same time or close to the date of s-25(OH) D determination.

2.4. Statistical analysis

Statistical evaluations were performed using SPSS 11(SPSS inc, Chicago, IL). The sample size was determined by the 90% power calculation described elsewhere [14]. Pearson's correlation coefficient was used to identify associations between the variables. The two arms were compared at baseline using students t test, and compared baseline with 3 phases by repeated measure analysis of variance (ANOVA). PostHoc Least Square Difference (LSD) was performed to identify the significant group for each significant variable on ANOVA. All statistical tests were performed two-sided with P-value <0.05 statistically significant. No data was credited for missing data, and analyzed as intent to treat.

3. Results

The demographic and nutritional characteristic of participants at baseline is presented in Table 1. There was no significant