Comparison of the Efficacy of Oral and Intramuscular Vitamin D Therapy in Obese Children with Vitamin D Deficiency

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Abstract

Introduction:

The efficacy of oral versus intramuscular (IM) vitamin D administration in obese children is debatable. The purpose of this study was to compare the efficacy of oral versus IM administration of a single dose of cholecalciferol (300,000 IU) in obese children with vitamin D deficiency.

Methods

In an open-label, randomized, and cross-sectional clinical study, 96 obese patients with vitamin D deficiency and body mass index (BMI) $> +2$ standard deviation scores (SDS) for their age and gender were recruited. Sixty-one children received a single IM dose of cholecalciferol (300,000 IU), while 35 children received an oral single dose of cholecalciferol (300,000 IU). At the initial clinic visit, baseline serum calcium (Ca), phosphorus (PO₄), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD) concentrations were measured. After 12 weeks, serum biochemical and hormone levels were determined. The study's primary endpoint was a change in serum 25OHD hormone levels.

Results

There was no statistically significant difference between the IM and oral groups and baseline in the median 25OHD levels (8 (4) vs. 10.3 (1.8) ng/mL) and PTH levels (70 (28) vs. 68 (22) pg/ml). Compared to the oral group, the IM group showed a statistically significant increase in the 25OHD levels (IM Δ 25OHD: 31 (10) vs. oral Δ 25OHD: 20 (6.7) ng/ml, $p < 0.01$), while the PTH levels were significantly reduced from their baseline levels (IM Δ PTH: 53.2 (31.5) vs. oral Δ PTH: 37.4 (27.2) pg/ml, $p < 0.01$).

Conclusion

In obese children, a single IM dose of vitamin D (300,000 IU) had a greater bioavailability than a similar dose given orally. Supplementation of vitamin D (300,000 IU), either IM or orally, was found to normalize 25OHD levels in vitamin D deficient obese children.

What Is Known

Obese patients with vitamin D deficiency are treated with different dose regimen via intramuscular or oral administration. There are rare clinical trials regarding vitamin D treatment efficacy on obese children with vitamin D deficiency and there is no consensus involved in vitamin D dose or administration route for obese children.

What is New

We compared efficacy of oral versus intramuscular (IM) 300000 IU single dose cholecalciferol treatment in obese children with vitamin D deficiency. Our study showed that the increment of 25OHD achieved was significantly higher in intramuscular group than oral group, though oral group had slightly higher baseline 25OHD levels than intramuscular group.

Introduction

Vitamin D deficiency is common in children, owing to the more frequent testing of serum 25-hydroxyvitamin D (25OHD) in clinics (1). Vitamin D deficiency is defined by a serum 25OHD level < 12 ng/mL (2). Serum 25OHD maintains normal serum calcium concentrations by increasing calcium absorption from the intestine or calcium mobilization from bone, which is required for musculoskeletal health (3). Vitamin D deficiency should be treated as it has been linked to infectious, autoimmune, endocrine, neoplastic, and cardiovascular diseases (3–5).

Vitamin D deficiency is more prevalent in obese children and adolescents (1). Obese children are more likely to be vitamin D deficient due to adipose tissue sequestration and sedentary, indoor lifestyles (6). Additionally, obese children may receive less vitamin D from food sources (7). Obese patients with vitamin D deficiency are treated with a variety of dose regimens administered intramuscularly or orally. Gheibi et al. established that obese children with vitamin D deficiency achieved an adequate level with a single dose of 600,000 IU of cholecalciferol administered intramuscularly (IM) (8). Arani demonstrated that obese patients improved following once-weekly oral vitamin D (50,000 IU) supplementation for six weeks (9). In patients with obesity, Imga et al. demonstrated that a continuous oral vitamin D3 regimen with a weekly loading dose was more effective than a monthly intramuscular regimen (10). There are few clinical trials examining the efficacy of vitamin D treatment in obese children with vitamin D deficiency, and there is no consensus regarding the vitamin D dose or route of administration for obese children. The purpose of this study was to compare the efficacy of oral versus IM administration of a single dose of cholecalciferol (300,000 IU) in obese children with vitamin D deficiency.

Methods

Study Group

This study enrolled 96 obese children with vitamin D deficiency. All participants were diagnosed between the ages of 5 and 18 years and were followed at the Balikesir City Hospital's outpatient clinic of the Pediatric Endocrinology Unit. Between November 2015 and March 2017, this cross-sectional clinical study recruited participants from the same geographic area at 39.64° latitude. Patients with serum calcium >10.8 mg/dl, serum phosphorus >5.5 mg/dl, recent calcium/vitamin D supplementation in the preceding 6 months, rickets other than nutritional, congenital or acquired bone diseases, dietary calcium intake exceeding 1500 mg/day, intestinal, renal or hepatic disorders, current cancer, ongoing multivitamin

intake, diabetes mellitus, current insulin or metformin supplementation, and use of sunscreen creams were excluded. At the time of presentation, demographic data, clinical characteristics, and laboratory parameters were obtained from the participants' parents and, when appropriate, from each participant. A detailed history was taken, including dietary calcium intake, a three-day dietary record, indoor lifestyles, and the amount and duration of sunlight exposure to specific body parts. The dietary calcium intake was calculated according to the Turkish Nutrition Guide (2015) (11). The examiner focused specifically on the presence of musculoskeletal findings during the history and physical examination. Regular sunlight exposure was defined as children being exposed to sunlight for at least 30 minutes per day for more than four days per week.

Study Design

The study design was an open-label, randomized, pre-and post-treatment comparison of the efficacy of oral versus IM administration of a single dose of 300,000 IU of cholecalciferol in obese children. Vitamin D supplementation (Devit-3 ampoule, Deva Drug Factory, 4. Levent, Istanbul, Turkey, contains 300,000 IU of vitamin D) was given orally or intramuscularly. At the initial clinic visit, anthropometric measures were assessed and recorded, as well as serum albumin, calcium (Ca), phosphorus (PO₄), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25OHD concentrations. After 12 weeks, serum biochemical and hormone levels were determined. The changes in serum Ca, PO₄, ALP, PTH, and 25OHD levels were compared between the IM and oral groups. The study's primary endpoint was a change in serum 25OHD levels.

Definition of exogenous obesity

Children were weighed barefoot and in light clothing on a digital scale (Seca Corp., Chino, CA, USA). Height was determined using the wall-mounted "Harpender" stadiometer, which is similar to the one designed by Tanner and Whitehouse. The body mass index (BMI) was then calculated (kg/m²), and the standard deviation scores (SDS) of the data were calculated using the Reference Values for BMI in Turkish Children (12). Children were classified as obese if their BMI was >+2 SDS for their age and gender (12). The examiner focused mainly on abnormal physical or endocrinological findings to rule out secondary causes of obesity, including monogenic obesity, hypothyroidism, growth hormone deficiency, Cushing syndrome, and pseudohypoparathyroidism.

Laboratory methods

After at least a 12-hour fast, blood samples were collected in biochemical tubes and centrifuged for 15 minutes at 2500 rpm. The sera were kept frozen at -20°C. Serum albumin, Ca, PO₄, and ALP levels were measured spectrophotometrically, while serum intact PTH was measured using a chemiluminescent microparticle immunoassay (CMIA; Abbott Architect Plus i1000SR). In addition, total serum 25OHD levels

were measured using an electro-chemiluminescence immunoassay (ECLIA) (Cobas e601 autoanalyzer, Roche Diagnostic GmbH, Mannheim, Germany). Serum 25OHD levels <12 ng/ml indicate vitamin D deficiency (2). The analytical measuring range was specified by the manufacturer as 3.00 to 70.0 ng/ml, with values below the detection limit are reported as <3.00 ng/ml, while values above the measuring range reported as >70.0 ng/ml. The intraassay coefficient of variations (CVs) were 2.2% and 6.8%, and the interassay CVs were 3.4% and 13%.

Ethical standards

The study was approved by the Research Ethics Board of Dr. Behcet Uz Children's Hospital in Turkey. The participants' parents gave written, informed consent. The investigations were conducted in accordance with the principles of the Helsinki Declaration.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 18.0. Categorical data were presented as percentages, numerical data with a Gaussian distribution as mean and standard deviation, and data with abnormal distribution data as median and interquartile range. The Chi-square or Fisher's exact test was used to compare proportions between groups, whereas the Student's t-test or Mann-Whitney U test was used to compare numerical data between groups. A p-value of less than 0.05 was considered statistically significant.

Results

All patients had white skin, and 61 received single IM dose of 300,000 IU of cholecalciferol, while 35 received single oral dose of 300,000 IU of cholecalciferol. Table 1 shows the Basic demographic characteristics of each group. Compared to the oral group, patients in the IM group had higher body weight (83 ± 22 vs. 73 ± 19 kg, $p = 0.036$) and BMI levels (33 ± 5.5 vs. 30.3 ± 3.7 , $p = 0.014$). The patients' dietary calcium intake ranged between 1200 and 1420 mg per day. Five had regular sunlight exposure, two had covered traditional dressing, 94% had sedantary, indoor lifestyles, and 7% had musculoskeletal signs (musculoskeletal pain, muscle weakness, and low physical activity). Serum albumin levels were normal in all patients. According to the Thacher radiographic scoring method, no rickets' findings were detected in the X-rays of the patients.

Table 2 shows biochemical and hormonal levels pre- and post-treatment. There was no significant difference between the IM and oral groups in baseline mean Ca level (9.6 ± 0.38 vs. 9.6 ± 0.38 mg/dl, $p = 0.92$), mean PO₄ levels (4.1 ± 0.72 vs. 4.3 ± 0.69 mg/dl, $p = 0.21$), and median ALP levels (217 (134) vs. 235 (141), $p = 0.15$), as well as baseline median 25OHD levels (8 (4) vs. 10.3 (1.8) ng/ml, $p = 0.12$), and median PTH levels (70 (28) vs. 68 (22) pg/ml, $p = 0.66$). Table 3 depicts changes in biochemical and hormonal levels. There was no significant difference between the IM and oral groups in the change in Ca

(IM Δ Ca: 0 (0.2) vs. oral Δ Ca: 0 (0.2), $p = 0.56$), PO4 (IM Δ PO4: 0.1 (0.3) vs. oral Δ PO4: 0.1 (0.3), $p = 0.76$), and ALP levels (IM Δ ALP: 26 (54) vs. oral Δ ALP: 33 (73), $p = 0.15$). However, throughout the observation period from the baseline, we found a statistically significant increase in 25OHD levels in the IM group compared to the oral group (IM Δ 25OHD: 31 (10) vs. oral Δ 25OHD: 20 (6.7) ng/ml, $p < 0.01$), while intact PTH levels were significantly decreased in the IM group compared to the oral group (IM Δ PTH: 53.2 (31.5) vs. oral Δ PTH: 37.4 (27.2) pg/ml, $p < 0.01$).

We analyzed the anticipated rate of median rise in serum 25OHD per kilogram. After 12 weeks, the anticipated rate of median rise in serum 25OHD was 0.38 (0.24) ng/ml/kg for IM cholecalciferol (300,000 IU) and 0.29 (0.17) ng/ml/kg for oral cholecalciferol (300,000 IU). The comparison of IM with the oral group showed a statistically significant difference ($p = 0.001$) (Figure 1). We also analyzed the anticipated rate of median rise in serum 25OHD per day. The anticipated rate of median rise in serum 25OHD was 0.34 (0.12) ng/ml/day for IM cholecalciferol (300,000 IU) and 0.22(0.08) ng/ml/day for oral cholecalciferol (300,000 IU) ($p < 0.001$) (Figure 1).

Discussion

In our study, the oral group had slightly higher baseline 25OHD levels than the IM group, but the IM group achieved a significantly higher increase in 25OHD levels than the oral group. For children aged 1 to 5 years, Shaikh et al. found that a single dose of 600,000 IU of cholecalciferol administered IM achieved a statistically significant higher range of serum 25OHD levels compared to oral administration of the same dose. In addition, this study suggests using the IM route for children suspected of having malabsorption (13). In a study conducted by Gupta et al., healthy adults were given either IM cholecalciferol (300,000 IU) or oral cholecalciferol (60,000 IU) weekly for five weeks, and the results showed that the IM group had significantly higher 25OHD levels than the oral group (14). Moreover, in older patients, Tellioglu et al. reported that older patients who received a single dose of 600,000 IU of cholecalciferol intramuscularly had a statistically significant increase in serum 25OHD levels compared to those who received the same dose orally (15). On the other hand, Cipriani et al. studied the bioavailability of oral or IM administration of a single dose of 600,000 IU of cholecalciferol in adults with vitamin D deficiency and found that both forms of vitamin D3 were effective in increasing serum 25OHD levels at day 90 of treatment (16). Cipriani et al. also reported that a single oral dose of 600,000 IU of cholecalciferol significantly increased 25OHD levels in healthy subjects (17). In 20 obese patients with vitamin D deficiency, Brar et al. showed that oral vitamin D (300,000 IU) therapy significantly increased 25OHD levels (18). Another study compared the effectiveness of oral administration of 2,000 IU cholecalciferol once daily for 12 weeks in obese and nonobese Caucasian adolescents and concluded that obese patients required higher cholecalciferol doses to treat vitamin D deficiency (19). At the first clinic visit, we advised our patients to consume vitamin D-rich foods and get regular sunlight exposure. The majority of them consumed these foods and were exposed to sunlight in order to increase their serum 25OHD levels. We assume that our patients' dietary vitamin D intake has been increased, but we are unable to distinguish between vitamin D derived from food and that derived from sunlight's effect on serum 25OHD levels. Although these foods and

sunlight exposure have an impact on our results, it is impossible to avoid recommending them to patients in clinics.

One study investigated the pharmacokinetics of the 25OHD response to three different doses of oral cholecalciferol in obese adults and found that 2.5 IU/kg of oral cholecalciferol was required for each unit increase in 25OHD level (ng/ml) (20). Heaney et al. reported that the anticipated rate of increase in serum 25OHD level was 7 ng/ml for each 1,000 IU/day of cholecalciferol administered orally (21). After 12 weeks, we established that the anticipated rate of increase in serum 25OHD level was 0.38 ng/ml/kg for each 300,000 IU of cholecalciferol administered IM and 0.29 ng/ml/kg for each 300,000 IU of cholecalciferol administered orally. Additionally, we found that the anticipated daily rate of increase in serum 25OHD in the IM group was significantly higher than that in the oral group.

Although vitamin D deficiency was prevalent in obese children, the prevalence of rickets was low, implying that it was a relatively rare disease in obese children (1,22). If adequate Ca and vitamin D are consumed, the Ca concentrations remain within the normal range. If Ca or vitamin D consumption is decreased, Ca concentrations may decrease (22-24). Due to the feedback mechanism, decreased Ca concentrations result in increased PTH secretion, lowering serum PO₄ levels by increasing PO₄ excretion in the urine (22-25). Decreased PO₄ levels cause rickets by inhibiting the apoptosis of hypertrophic chondrocytes (24,25). We found no evidence of rickets in 96 obese children with vitamin D deficiency due to their adequate Ca intake. These patients exhibited increased hunger or decreased satiation, suggesting that they may be at a lower risk of acquiring rickets. Moreover, our patients exhibited fewer musculoskeletal manifestations owing to adequate calcium intake. We expected obese children to have fewer musculoskeletal manifestations of vitamin D deficiency than nonobese children because they are more likely to get enough calcium from foods due to increased hunger or decreased satiation.

Vitamin D deficiency has been linked to a variety of disorders, including insulin resistance, type 2 diabetes, polycystic ovarian syndrome, and non-alcoholic fatty liver disease, as well as autoimmune and neoplastic diseases (3–5). Obese children are more likely to have these disorders as a result of their increased fat tissue. To avoid these disorders, serum 25OHD levels in obese children should be maintained above 20 ng/dl (2,26). Samaranayake et al. investigated the effects of vitamin D supplementation on obesity-related parameters, including anthropometric measures, body composition, and metabolic profiles in obese Sri Lankan children with vitamin D deficiency, and found that a high dose of vitamin D improved these parameters (26). Moreover, Aliashrafi et al. evaluated the efficacy of vitamin D supplementation on glucose homeostasis, insulin resistance, and matrix metalloproteinase levels in obese subjects with vitamin D deficiency and found that improving vitamin D status resulted in greater weight loss and a reduction of matrix metalloproteinase levels (27). Furthermore, Rajakumar et al. reported that optimizing the vitamin D status of obese children may improve their cardiovascular health (28). We found that supplementation with a single dose of 300,000 IU of cholecalciferol administered IM or orally normalized 25OHD levels in our obese patients. However, we were unable to follow these parameters in our patients. On their second clinic visits, the majority of children in our study felt well-

being, and their guardians requested that the treatment be continued. Both routes for administering a 300,000 IU dose of cholecalciferol resulted in 25OHD levels within the normal range in our region.

Compliance is critical to achieve the 25OHD target level in children. For maximum efficacy, oral cholecalciferol supplementation should be regularly administered on a daily or weekly basis.

Single oral or IM doses of vitamin D may be a practical choice for treating children with vitamin D deficiency.

One of the strengths of our study was the pre-and post-comparison design, which eliminated confounding variables such as ethnicity, age, gender, or season. Another strength of our study was the inclusion of children with a broad range of BMI SDS values in the obese range, including those with extreme obesity, defined as a BMI SDS as high as 4.4 for age and gender. Prior to treatment, we also assessed nutritional Ca intake, sunlight exposure, and musculoskeletal findings.

Although our sample was relatively small for a post-comparison study in obese children, we revealed for the first time that supplementing with a single dose of 300,000 IU of cholecalciferol intramuscularly resulted in a greater increase in 25OHD levels than a single oral dose. This study would be interesting if we considered vitamin D intake during the observation period. Another limitation in our study is that the number of patients in the IM group was nearly double that of the oral group since most obese children with irritable bowel syndrome refused to receive oral vitamin D due to nausea and epigastric pain. Another limitation of our study was the inability to assess bone turnover markers and, consequently, the state of skeletal health. Our study was not designed to determine the pharmacokinetics of 25OHD response to treatments, which depend mainly on genetic factors, including 24-hydroxylase and 25-hydroxylase activity, as well as vitamin D-binding protein synthesis (29-32).

In conclusion, our findings show that the IM group had higher bioavailability than the oral group. Administration of a single dose of vitamin D (300,000 IU), either IM or orally, was found to normalize 25OHD levels in vitamin D deficient obese children.

Abbreviations

Alkaline phosphatase (ALP)

Body mass index (BMI)

Calcium (Ca)

Coefficient of variations (CVs)

Electro-chemiluminescence immunoassay (ECLIA)

25-hydroxyvitamin D (25OHD)

Intramuscular (IM)

Parathyroid hormone (PTH)

Phosphorus (PO₄)

Standard deviation scores (SDS)

Declarations

Conflict of interest: The authors declare there is no conflict of interest in this paper.

Data available on request from the authors

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

The investigations conformed to the principles outlined in the Declaration of Helsinki.

The study was approved by the Research Ethics Board of Dr. Behcet Uz Children's Hospital in Turkey. The participants' parents gave written, informed consent.

Authors' contributions:

Concept, Design, Analysis or interpretation, Writing: Huseyin Anil Korkmaz, Behzat Ozkan

Data collection, Literature research: Utku Karaarslan

Informed consent was obtained from legal guardians.

There is no individual's data or image for publication of our study.

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Tables

Table 1. Bazal demographic characteristics of obese patients with vitamin D deficiency

	IM 300000Ü	Oral 300000Ü	P
Age(years)*	12.9±2.8	12.9±2.7	0.25
Gender F/M	44/17	26/9	0.81
Weight (kg)*	83±22	73±19	0.036
Weight-SDS**	2.9(1.2)	2.7(1.1)	0.073
Height(cm)*	156±14	152±14	0.11
Height-SDS**	0.5(0.9)	0.34(1.5)	0.78
BMI*	33±5.5	30.3±3.7	0.014
BMI-SDS**	2.85±0.61	2.64±0.49	0.075
Gestational age (week)*	38.4±1.9	38.6±1.5	0.58
Birth weight (gr)**	3500(850)	3400(750)	0.65
Vitamin D prophylaxis (-/+)	22/39	12/23	0.86
Nutrition Breastfeeding /Formula	18/43	5/30	0.093
* Variables are shown as mean± standart deviation			
** Variables are shown as median (interquartile range)			
BMI: Body mass index			

Tablo 2. Biochemical and hormonal levels before and after treatment in obese patients

	IM 300000Ü		Oral 300000Ü	
	BT	AT	BT	AT
Calcium(mg/dl)*	9.6±0,38	9.6±0,37	9.6±0,38	9.6±0.32
Phosphorus (mg/dl)*	4.1±0.72	4.2±0.61	4.3±0.69	4.3±0.5
ALP (IU/L)**	217(134)	180(79)	235(141)	184(82)
25OHDvit (ng/ml)**	8(4)	39(10)	10.3(1,8)	29(4.6)
PTH(pg/ml)**	70(28)	16(10)	68(22)	27(14)

* Variables are shown as mean± standart deviation

** Variables are shown as median (interquartile range)

BT/AT Before treatment/After treatment

Tablo 3. Change in biochemical and hormonal levels in obese patients

	IM 300000Ü	Oral 300000Ü	P
Δ Calcium (mg/dl)	0(0.2)	0(0.2)	0.56
Δ Phosphorus (mg/dl)	0.1(0.3)	0.1(0.3)	0.76
Δ ALP (IU/L)	26(54)	33(73)	0.15
Δ 25OHDvit (ng/mL)	31(10)	20(6.7)	<0.01
Δ PTH (pg/ml)	53.2(31.5)	37.4(27.2)	<0.01
Variables are shown as median (interquartile range)			

Figures

Figure 1

Legend not included with this version