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Impact of Dietary Status on The Effectiveness of Vitamin D Supplementation in Children with Severe Vitamin D Insufficiency

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Original Article

Abstract

Background: *Vitamin D has always been known as the sunshine vitamin. Initially considered an essential nutrient and classified as a fat-soluble vitamin, over the years it has been recognized as a complex fat-soluble prohormone that is metabolized into a true hormone.*

Objective: *The objective of this study is to evaluate the prevalence of severe vitamin D deficiency in children and investigate how dietary status affects the response to supplementation.*

Method: *A prospective open-label intervention study carried out between the end of May and the beginning of June 2022 with convenience sampling in children between 8 and 10 year olds. The children were summoned on a 10-hour fast to join the protocol.*

Results: *A total of 108 children were studied, with equally gender distribution, average age of sample was 9.6 ± 0.5 years. 39% were eutrophic. The average of 25-hydroxyvitamin D was 10.8 ng/ml: 96.2% had deficiency and 3.8% insufficiency. Severe deficiency was investigated by 64%. The basal concentration of 25OHD did not vary according to nutritional status. Then of supplementation, the mean 25-hydroxyvitamin D was 17.3 ng/ml: 36% insufficient, 62% deficient, and 2% sufficiency. Those with weight excess had a significant 25OHD upsurge less than eutrophic children. Children with weight excess would require doses of VD 32% higher than eutrophic children to achieve the same concentration of 25OHD.*

Conclusion: *high prevalence of weight excess, and deficiency of VD and most in severe deficiency range. Weight excess interferes with the response to pharmacological supplementation, achieving a lower increase of 25OHD*

Keywords: *Vitamin D, Weight excess, children.*

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1. INTRODUCTION

Vitamin D (VD) is a pleiotropic hormone that is synthesized on the skin from cholesterol precursors or, in smaller measure, acquired in the diet from rich foods in VD. The most well-known role of the VD it is in the maintenance of the homeostasis of bone metabolism (1). However, this hormone has multiple actions biological in almost all organs and systems of the body human. Its deficiency has been associated with increased mortality and multiple illnesses, including infections respiratory, cancer, autoimmune diseases, allergies and cardiovascular diseases (2). There has been a growing focus on studying the cellular metabolism and physiology of vitamin D in the past few years. Furthermore, it is regarded as a prohormone that plays a crucial role in maintaining the balance of bone tissue. Various international studies have documented an increase in the prevalence of vitamin D insufficiency, which is defined as having blood levels of 20 ng/ml or 50 nmol/l or lower. The occurrence of this insufficiency has been found to range from 10% to 41.6% in investigations that involve studying the general population (3). Vitamin D is a group of prohormones that were identified following the discovery of the advantageous impact of cod liver oil in preventing rickets in the early 20th century. The two main biologically inert precursors are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) (4,5) . Vitamin D3 is synthesized when 7-dehydrocholesterol in the skin is exposed to ultraviolet B rays (UVB 290 to 320 nm) from the sun, and it is then transformed into previtamin D3. Vitamin D is generated from previtamin D3 by a mechanism that is dependent on heat (6). Conversely, vitamin D2 is obtained from plants and is created externally by exposing ergosterol to radiation. It then enters the bloodstream through the diet (7). Within our body, both D2 and D3 precursors undergo an initial hydroxylation process in the liver, resulting in the formation of 25-hydroxyvitamin D [25(OH)D]. This metabolite is then analyzed in the blood to identify the quantities of vitamin D present. The conversion of 25 (OH)D to 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol, requires a second hydroxylation process at the renal level. Calcitriol is the active form of this vitamin (8). Vitamin D is essential for regulating blood calcium and phosphorus levels. In the absence of this vitamin, the body would only absorb between 10 and 15% of the calcium consumed through diet and approximately 60% of the phosphorus. Vitamin D significantly impacts the process of bone production and upkeep (9). The Institute of Medicine (IOM) committee

updated their guidelines for vitamin D consumption in the general population in 2010. The recommendations provided criteria for the optimal upper limit of vitamin D in the bloodstream (to maintain it below 50 ng/ml or 125nmol/l) and the definition of deficiency (below 20 ng/ml or 40nmol/l, which is the level required by 97.5% of healthy adults). To enhance peak bone mass, prevent bone loss, and decrease the likelihood of fractures resulting from osteoporosis, it is recommended to maintain serum vitamin D levels above 20 ng/ml (10,11). The IOM study outlines the recommended daily consumption of vitamin D for healthy children, specifically advising that children over the age of 1 should consume 600 IU per day. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPAGHAN) recommends that infants below the age of one should be given a daily oral supplement of 400 IU under the guidance of a healthcare practitioner. It is important for children and adolescents to have a nutritious diet and engage in a healthy lifestyle that includes consuming foods that are high in vitamin D. Nevertheless, children who are deemed to be at danger of experiencing a deficit, such as those with dark skin, limited sun exposure, or obesity, should be provided with an oral supplement. According to the ESPGHAN, serum vitamin D levels above 50 nmol/l are considered adequate, whereas levels below 25 nmol/l are categorized as severe deficient (12).

2. PATIENTS and METHODS

A prospective open-label intervention study was conducted of nutritional supplementation with VD3 as convenience sampling in children between 8 and 10 year olds. Those who voluntarily wanted to participate they signed an informed consent from their parents and were applied a survey to obtain information from the child: date of birth, time of residence in the region, diseases and treatments received in the last 6 months, use chronic of medications, use of vitamins in the last 6 months and travel outside the region in the last 6 months. It they included apparently healthy children who did not present some of the following exclusion criteria: chronic diseases in treatment, vitamin D supplementation in the 6 months before entering the study. The children were summoned on a 10-hour fast to join the protocol, between the end of May and the beginning of June 2022. The children were weighed down with clothes light on an electronic scale and were measured barefoot with Dry brand stadiometer, following international standards anthropometric. The anthropometric assessment it was carried out according to the WHO 2007 anthropometric standards. Using the Growth Analyzer version 3.5

program it was determined Z-score of size/age (ZT/E) and Z-score of index of body mass/age (ZIMC/E) according to sex and age. Was diagnosed low weight with less than ---2 standard deviations (SD) of ZIMC/E, eutrophy between ---1.9 to +1 SD, overweight between +1 and +1.9 SD and greater obesity to +2 SD.

The diagnosis of WE includes all children with ZIMC/E > + 1 SD.

Blood sample was taken by venepuncture, protected of the light. In a refrigerating unit, the samples then send to the laboratory of the our hospital to investigate the blood level of calcium, Phosphorus, the alkaline phosphatases (AP) and parathyroid hormone (PTH). The sample for 25OHD was frozen and stored in the same laboratory. Then the samples for frozen 25OHD were sent to the Hormone Analysis Laboratory where they were processed using a commercial ELISA Diasource (Louvain-la-Neuve, Belgium).

This methodology allows the simultaneous measurement of 25OHD D2 and D3; the sensitivity of this assay is 1.5 ng/ml, with an intra-assay Coefficients of Variability (CV) of 1.5% and an inter-test CV of 5.9%). The results were obtained, each proxy was sent an information note with child's results along together with 60 tablets of vitamin D3 /800 IU vitamin D3 tablets, with the indication of giving 2 tablets daily (1,600 IU) for a month. The dose to be supplemented was chosen in line with recommendations of clinical practice guidelines that state that to achieve optimal serum levels of 25OHD in children is it requires supplementation with at least 1,000 IU a day of D3 (13).

Since the presentation of the available VD3 capsules contained 800 IU was chosen to be supplemented with 2 capsules daily for a month. The chosen dose was under the limit superior tolerable journal instituted by the Institute of Medicine of the United States National Academy of Sciences for the age of the study group. The duration of the study of one year was chosen to facilitate follow-up and optimize adherence to the treatment of children. All the children they were supplemented with VD3. Adherence to the treatment was recorded by questionnaire and proceeded to take the children the second blood sample only for determination of 25OHD, the which was frozen and stored in the hospital laboratory to be subsequently sent to the Hormone analysis laboratory.

This work was approved by the Ethics Committee of Research of the our hospital and ministry of health.

Statistical analysis

The normality of variables was analyzed by means of test from Kolmogorov-Smirnov. The results are reported as average ± standard deviation (SD) for normal variables. The baseline measurement of 25OHD showed no distribution normal, so it is reported as median (range). Differences between subgroups were analyzed by the proof "t" of Student with 2 tails or Mann-Whitney test for non-parametric variables. The correlation between variables was evaluated by means of a bivariate correlation of Pearson. The dose-response slope of 25OHD was calculated dividing the difference of 25OHD before and after the supplementation by the daily dose of cholecalciferol in micrograms, as previously described.

A value $p < 0.05$ was considered significant in all analyses. The statistical analysis was performed with the SPSS Statistics software version 26.0 (IBM Corporation, Armonk, NY).

3. RESULTS

A total of 108 children were included in the study. The baseline demographic, nutritional and laboratory characteristics of the studied population are shown in Table 1. The median 25OHD was 10.8 ng/ml with a range of 4.3- 28,4. 25OHD deficiency (<20 ng/ml) was observed in the 96.2% of children and insufficiency (20 to 29 ng/ml) in 3.8%. Severe deficiency (<12 ng/ml) was detected in 64%. No there were children with sufficient 25OHD levels (>30 ng/ml). there was No significant correlation between 25OHD and PTH, phosphemia or Alkaline phosphatase, but there is a weak significant correlation between higher 25OHD and lower calcemia ($R = -0.25$, $p = 0.01$). There were no differences by sex in none of the parameters studied. The basal concentration of 25OHD showed no variation according to the nutritional status. Children who travelled outside the region in the last 6 months had a higher concentration of 25OHD than those who remained in the region (12,7 [10,6-16,1] vs 10.7 [9.7-13], $p = 0.005$), however, 94.4% of them were in the deficient range anyway. 87 children completed the study (80.6% of the sample) who reported having taken the indicated doses of VD3. The 21 children who did not participate in the second measurement it was due to non-attendance at school on evaluation days. The children who did not have follow-up were not significantly other than those who completed the study as soon as to sex, age, ZIMC/E, ZT/E, basal level of 25OHD or other laboratory parameters (all variables, $p > 0.05$). After supplementation, a median of 25OHD of 17.3 ng/ml (range 8.4-33.8), which was higher to that

found in the first sample ($p < 0.001$). Then of the VD3 supplementation, 62.1% was in deficiency range (14.9% with severe deficiency), 35.6% with insufficiency and only 2 children (2.3%) presented sufficient (> 30 ng/ml). After the supplementation the children eutrophic showed a 25OHD of 19.7 ng/ml (range 9.8- 33.8) and children with Weight excess had a 25OHD of 16.2 (range 8.4-29.5), which had a significant difference ($p < 0.03$). A smaller increase in the concentrations of 25OHD in children with Weight excess compared to children eutrophic (5 ± 5.5 vs. 7,7 ± 4.9, $p = 0.03$). The slope of increase of serum 25OHD was 0.13 ± 0.14 ng/ml/g/day in children with Weight excess compared to 0.19 ± 0.12 ng/ml/g/day in eutrophic children ($p < 0.03$). The reason for both pending results in a 32% higher VD3 requirement in children with WE to achieve the same effect as in children with state normal nutritional.

Table 1. Demographic, anthropometric and laboratory basal areas of the children studied

Variable		No.	%
Total number of patients		108	100.0
Sex	Male	54	50.0
	Female	54	50.0
Age (years), mean ± SD		9.6 ± 0.5	-
Z-score height/age, mean ± SD		+ 0.1 ± 0.86	-
Z-score of BMI/age, mean ± SD		+ 1.17 ± 0.84	-
Eutrophy		-	38.9
Overweight		-	46.3
Obesity		-	14.8
25(OH)D (ng/ml), median (range interquartile)		10.8 (10.2-12.8)	-
Calcium, mg/dl		9.6 ± 0.2	-
Phosphorus, mg/dl		4.7 ± 0.6	-
Alkaline phosphatases IU/l		261 ± 59	-
Parathormone, pg/ml		45 ± 12	-

Z: standard deviation score; 25OHD: 25-hydroxy-vitamin D.

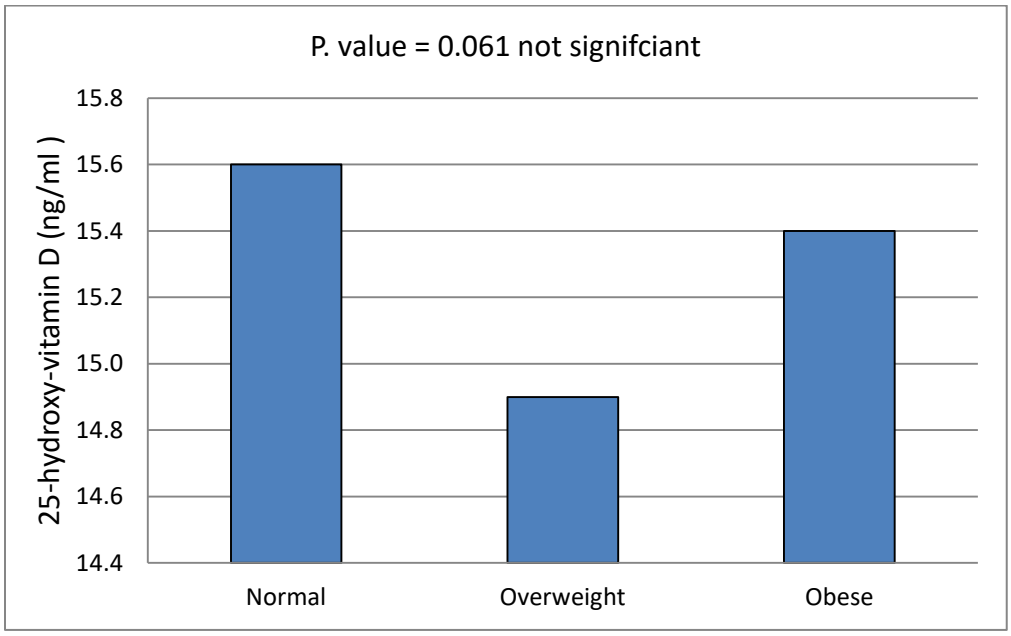

Figure 1. Basal concentration of 25-hydroxyvitamin D according to the nutritional status of children

4. DISCUSSION

The present study reports a very high prevalence of deficiency of vitamin deficiency in children in the area of the study, with a very important fraction of children in severe deficiency ranges. The 25OHD levels of this population are more lower than those observed in 60 preschool children, in which a 64% of children with a deficiency (<20 ng/ml) and that 155 school healthy of both sexes in a study carried by Arteaga M et al, who showed an average of 25OHD of 21.1 ± 0.7 ng/ml and 56% of low levels 20 ng/ml5 (14). Karagol C, and his colleague found that the prevalence of vitamin D deficiency and insufficiency was to be 18-24.9% in healthy children (15). The levels of VD deficiency of the children are comparable with those registered by Oliveri et al. in ninos de Ushuaia, Argentina, city that it is located at a similar latitude (16). VD deficiency has been associated with a multiplicity of human diseases, so the fact that that the greater part of the national population of Santiago at having poor levels from an early age can have significant public health consequences for the country. Moreover, the levels of severe deficiency observed in most of children studied place even greater urgency for the people of the Magellan. Studies of various diseases have been showing that, and in particular in the of Iraqi child highest rates of diseases that have been associated with VD deficiency in other latitudes (17). There is a high prevalence of vitamin D insufficiency among

youngsters between the ages of 6 and 12. The seasons of Spring and Winter pose significant risks for the development of vitamin D insufficiency (18). In U.S. children and adolescents. USA. it has been found greater deficiency of VD to greater WE, being found 49% of VD deficiency in those with severe obesity compared with 21% in those who have eutrophy as a diagnosis nutritional (19). However, this study was conducted in a multiracial sample from the state of Texas, with levels of VD deficiency much lower than those recorded in the present study, at the Iraqi children's no association was found between VD deficiency with nutritional status at baseline measurement. This could be explained because of the high prevalence of severe deficiency he had this cohort prior to supplementation that may it does not allow to observe these differences.After supplementation, children with WE of the this study showed lower concentrations of 25 OHD than the eutrophic children. The lowest rise of 25OHD following the supplementation of VD in children with WE is he has described in adult population and recently in population paediatric, it is still to be defined how it should be supplementing people with WE (20). Dhaliwal et al. they studied differences in responses to supplementation with VD in obese adults with BMI > 35 compared to adults with a BMI < 35. In this study it was reported that the obese would require a 40% higher dose of VD to achieve the same final concentration of 25OHD (21). Our studio it shows slightly lower results than Dhaliwal et al., with a 32% higher dose requirement of VD3 to achieve the same final concentration of 25OHD in children with WE compared to eutrophic children. There are only 2 previous studies that evaluated the response a supplementation with VD3 in children according to their nutritional status. Rajakumar K,et al. they compared 21 obese children vs. 20 non-obese African-American children 6 to 10 years old who received 400 IU/day of VD3 for one month (22). However, less than 50% of the children in this study were deficient of VD basally, with an average 25OHD of 22.2 ng/ml in obese and 25.9 ng/ml in non-obese. There were no differences significant between obese and non-obese in the increase of 25OHD nor in the percentage of children who remained with VD deficiency after supplementation (22). Aguirre Castaneda et al. they studied 18 teenagers. obese and 18 non-obese adolescents paired by age and gender who in an open-label interventional study received 2,000 IU/day of VD3 for 12 weeks13. In line with our results, in this study do report a significantly smaller increase of 25OHD subsequent to the supplementation in the obese group vs. not obese (change of 5.8 vs.

9.8 ng/ml; p = 0.019). The Study of Aguirre Castaneda et al. reflects in its result a requirement 40% higher VD 3 in obese adolescents than in non-obese (20), identical result to that of Dhaliwal et al. The difference of this figure of 40% vs. 32% in our study could be explained in which the previous studies included subjects obese vs. not obese, and in the present study, on the other hand, he compared WE children vs eutrophic children (20). Children with WE of our study include overweight and obesity, and therefore probably a lower percentage of fat on average than subjects included in other studies. Since the VD is a lipophilic hormone, it is likely that the older the obesity and fat percentage, the higher the sequestration of VD in that compartment and lower the slope of upward of 25OHD circulating. This increased VD3 requirement in subjects with WE is very relevant at the time of deciding public health policies of supplementation with VD, given the high prevalence of paediatric and adult population with WE in the southern regions of our country. Other studies have also shown an association significant between VD deficiency with the presence of alterations metabolic factors secondary to excess fat mass body that develops in the states of overweight and obesity (23). It is being studied whether supplementation of VD can improve metabolic alterations associated to obesity, such as dyslipidemia and insulin resistance in different populations, with the ultimate aim of preventing cardiovascular diseases in adulthood. Studies recently randomized placebo-controlled performed in pediatric population have shown improvement in insulin levels, HOMA index and levels of triglycerides (24,25), although other researchers have not shown significant improvement (26).

5. CONCLUSIONS

School children have a high percentage of WE, VD deficiency and most of them in the range of severe VD deficiency. We interferes with the response to supplementation pharmacological, achieving a lower increase of 25OHD. The children with WE would require a 32% higher dose of VD3 to achieve the same final concentration of 25OHD as children eutrophic. Additional studies are required to determine the potential consequences of VD deficiency in the health of the Iraqi child population of and the role of VD supplementation in the treatment of these.

Ethical Clearance:

Ethical issues were taken from the research ethics committee. Informed consent was obtained from each participant. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

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