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CLINICAL EXPERIENCE

Vitamin D concentrations in children and adolescents with celiac disease

Concentraciones de Vitamina D en niños y adolescentes con enfermedad celíaca

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Abstract

Introduction: In children with celiac disease, gluten intake causes an autoimmune, inflammatory and progressive lesion of the small intestine villi, compromising the absorption of nutrients and possible damage to others organs. **Objective:** To determine plasma 25-hydroxyvitamin D [25(OH)D] concentrations in Chilean child and adolescents with celiac disease. **Patients and Method**: A descriptive cross-sectional study was carried out in which 16 pediatric patients of both genders diagnosed with celiac disease participated. General background, nutritional status and biochemical parameters were determined. Plasma 25(OH)D concentrations were classified as sufficient between 30-100 ng/ml, insufficient between 20-30 ng/ml and deficient as <20 ng/ml. **Results**: The age of the patients was between 5 and 18 years (age: 11 ± 4 years). Four out of 16 participants had normal 25(OH)D concentrations, eight had insufficient concentrations and one had deficient concentrations. According to BMI, 11 patients had normal nutritional status, four were overweight and one was obese. In relation to height, seven out of 16 cases presented short stature and normal-low height. Associating 25(OH)D concentrations to nutritional status, nine patients with normal nutritional status, two with overweight and one with obesity presented deficient and insufficient parameters. No significant associations were found between 25(OH)D concentrations and all studied variables. **Conclusion:** A high frequency of insufficiency and deficiency of 25(OH)D was found in the group of Chilean children and adolescents with celiac disease.

Keywords:
Celiac disease; vitamin D; children; adolescents; nutritional status

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Introduction

Celiac disease (CD) is a chronic autoimmune condition, which affects mainly the small intestine in genetically susceptible individuals[1]. The CD is an increasingly common disorder in both childhood and adulthood with a prevalence of 1% to 3% in the Western population, and it is considered that for each diagnosed patient there are other five non-diagnosed patients with CD[2].

Its etiopathogenesis is the result of gluten intake, which is a group of proteins that are present in cereals, such as wheat (gliadin), rye (secalin), barley (orcein), triticale, kamut, and spelt. In the CD, a severe decrease in the nutrients absorption occurs, this deficiency would appear as a involvement of multiple tissues and systems, therefore, it becomes relevant in the child population due to its fast development and growth[2,3].

In childhood, the CD classic presentation is characterized by intestinal disorders, such as chronic diarrhea, abdominal distention, chronic vomiting, recurrent abdominal pain, rectal prolapse, and constipation. However, the non-classic presentation with extraintestinal manifestations is becoming more frequent, including stomatitis, endocrine, hepatic, neurological, dermatological, hematological, and dental alterations, and short stature[4,5].

In the classic CD presentation, it is common to find malabsorption syndromes, which causes a deficiency of certain micronutrients[6]. Iron deficiency anemia is one of the most common hematological disorders due to the iron deficiency[2,4]. However, the prolonged deficiency of vitamin D (vitD) has been less studied, which causes bone mineralization alterations, leading to rickets in children, osteopenia in adults and children, osteomalacia and osteoporosis mainly in adults[7]. In the last decade, the extra-bone roles of this vitamin have been discussed, since the characterization of the vit D metabolic pathway has demonstrated that its active form regulates the transcription of genes involved in adipogenesis, inflammation, and adipose tissue insulin resistance. The vit D has also been related to a potential role in autoimmune processes[1].

In the study conducted in Spain and Israel with children and adults with CD, Lerent et al. found that plasma 25-hydroxyvitamin D [25(OH)D] concentrations negatively correlated with age but not with intestinal damage, the older, the lower the 25(OH)D concentrations. According to this finding, there was no evidence of vit D deficiency in the pediatric population with CD[1]. A possible explanation is that the vit D deficiency in children and adults with CD would not depend exclusively on its gastrointestinal absorption, but also on the endogenous production of it, specially vitamin D3, which is formed from the exposure of 7-dehydrocholesterol in the skin through the solar ultraviolet-B rays transforming it into previtamin D3[8].

So far, there is only one Chilean report published in 2003, where 25 celiac children were studied (aged from 5 to 15 years), who had low plasma concentrations of vit D[9]. Since there is a lack of bibliographic information found in the Chilean children population, the objective of this study was to determine plasma concentration of 25(OH)D in Chilean children and adolescents with CD.

Patients and Method

Patients

Descriptive cross-sectional study, with a convenience sample of 16 children and adolescents of both genders, aged between 5 and 18 years, with confirmed CD diagnosis according to the Clinical Guide for Celiac Disease of the Ministry of Health (MINSAL), 2015[10], from Concepción. Children and adolescents from the Pro Celiac Patient Corporation (*Corporación Pro Paciente Celíaco*) of the University of Concepción who met the inclusion criteria were invited to participate during August and September 2015. People without a confirmed CD diagnosis were excluded.

Nutritional status evaluation

The measurements were made using standardized techniques by a trained nutritionist. For weight and height, a balance beam scale (Seca 700) was used. With this data, the BMI-for-age and height-for-age (H/A) indexes were determined. The WHO 2007 references were used for their evaluation[11]. The nutritional status classification was performed according to the Chilean ministerial regulation, using the qualification criteria according to the BMI expressed in SD, considering malnutrition ≤ -2 SD, at risk of malnutrition between ≤ -1 and -1.9 SD, eutrophy (normal) between +0.9 to -0.9 SD, overweight between ≥ + 1 to + 1.9 SD and obesity ≥ + 2 SD. The height qualification criteria according to H/A expressed in z-score considering short stature ≤ - 2.0 SD, low normal height between -1.0 and 1.9 SD, high normal height between +1.0 and +1.9 SD, and high height ≥ + 2 SD[12].

Body circumferences and skinfolds were measured with an inextensible metric tape and a skinfolds caliper (LANGE). With these data, the arm muscle circumference (AMC), arm muscle area (AMA), and arm fat area (AFA) were determined. The classification of the fat and muscle compartments were performed according to what was proposed by Frisancho[13]. The fat mass percentage (FM%) was determined by the Westrate and Deurenberg equations[14] and it was compared with the values proposed by the Freedman classification[15]. In order to assess the presence of abdominal obesity, the waist circumference (WC) was measured. For the measurement and classification technique, the Fernández references were used[16].

Biochemical tests

The tests were performed in the period between August and October 2015 (spring in the southern hemisphere), in the Central Clinical Laboratory of the *Clínica Sanatorio Alemán of Concepción*. Blood samples were obtained in the early morning hours, with a 10-hour fast. The samples were centrifuged and the plasma extracted in order to analyze it immediately. Hematocrits and hemoglobin, glutamic oxaloacetic transaminase (SGO-T), and serum pyruvic glutamic transaminase (SGP-T) were determined through Vitros 5600 analyzer. Immunoglobulin A (IgA) was determined through the Turbidimetric Method, the anti-transglutaminase antibodies (ATA) through the enzyme immunoassay technique (EIA). The normality parameters for the analyzed tests are available according to Fuentes 2012[17]. The plasma 25(OH)D concentrations, which were evaluated through the Enzyme-Linked Immunosorbent Assay (ELISA), Mini VIDAS, which measures the total vit D concentrations (25 OH D_2 + 25 OH D_3) and their hydroxylated metabolites. Plasma 25(OH)D concentrations were classified as sufficient when they were between 30 to 100 ng/ml, insufficient if 20-29 ng/ml, and deficient if < 20 ng/ml[18].

All patients were invited to participate in the research through the treating physician related to the project and/or a nutritionist from the Corporation. This study was approved by the Ethics Committee of the University of Concepción, and we had the signed informed consent from the patients and/or parents and/or caregivers.

Statistical analysis

The obtained results through the performed assessments were input to an Excel file, which was analyzed with STRATA v12 software. The variables were represented by their median (SD) when they verified the assumption of normality (Shapiro-Wilk test), otherwise, their median was specified (p25-p75). For the association between quantitative variables, the Pearson (Spearman) correlation coefficient was used, and for qualitative variables, the Fisher exact test was used. The t-Student test was used to perform comparisons between two groups (vit D average in men and women). A 0.05 significance level was used.

Results

Out of the 16 pediatric patients, three were male and 13 were female, one preschooler, nine scholars and seven adolescents, with an average age of 11.04 ± 4 years (Table 1). According to the BMI, 11 children and adolescents had a normal nutritional status, four had overweight, and one had obesity. The height diagnosis showed seven cases of short stature and low normal height (Table 2). The fat and muscle compartments were mostly normal and only one patient had an increased FM% (Table 3).

Table 2 shows that four out of 16 patients had sufficient plasma 25(OH)D concentrations, eight had insufficient and four had deficient concentrations.

Table 1. Baseline characteristics of patients. Data expressed as mean (DS) and median (Q1-Q3), percentage or current number

Characteristic	n = 17
Age (years)	11.04 (4.04)
Age at diagnosis(years)	6.86 (5.72)
Disease duration (years)	4.18 (3.34)
Anthropometric Parameters	
BMI (z-score)	0.55 (0.92)
Height/Age (z-score)*	-0.51 (-1.17- -0.14)
Biochemical Tests	
Vitamin D (ng/ml)	24.7 (10.7)
GOT (U/l)*	26.5 (21.0-30.02)
GPT (U/l)*	25.5 (21.0-29.0)
Hemoglobin (gr/%)	13.2 (1.1)
Hematocrits (%)	38.9 (2.9)
Inmunoglobulin A (mg/dl)	137.2 (46.0)
Antitransglutaminase (U/ml)* (n = 14)	2.9 (1.5-3.0)

*They do not have normal distribution. BMI: Body Mass Index. GOT: glutamic oxaloacetic transaminase. GPT: Piruvica transaminase.

Table 2. Status Nutritional and concentrations of 25OHD D

	Frecuency (n)	%
Anthropometric parameters		
BMI/Age (z-score)		
Eutrophy	11	68.75
Overweight	4	25.00
Obesity	1	6.25
Height/Age (z-score)		
Low	4	25.00
Low Normal	3	18.75
Normal	7	43.75
High Normal	1	6.25
High	1	6.25
Biochemical tests		
Vitamin D (ng/ml)		
Sufficient	4	25.00
Insufficient	8	50.00
Deficient	4	25.00

BMI: Body Mass Index.

Table 3. Indicators of Body Composition of patients

	Normal (n)	High (n)	Low (n)
Arm Muscle Area	11	1	4
Arm Muscle Circunference	11	1	4
Arm Fat Area	13	3	0
Tricipital Skinfold	14	2	0
	Normal (n)	Moderate (n)	High (n)
% Fat Mass	7	8	1

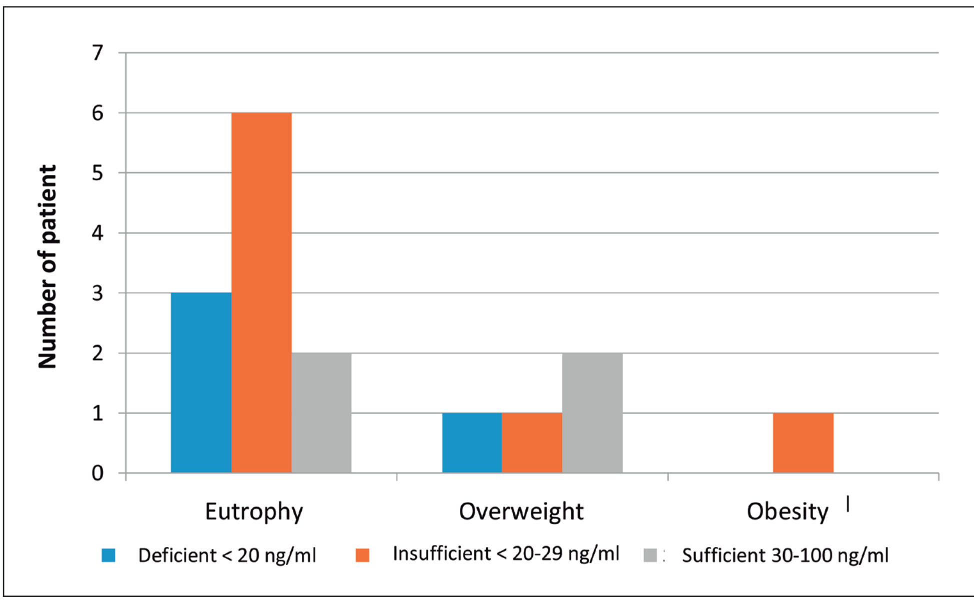

Figure 1. 25 OHD plasma concentrations according to nutritional status.

Regarding hematocrit, the values ranged from 34% to 43%, presenting only one case under normal values according to his/her age. With regard to SGO-T and SGP-T, only one patient in the sample had higher-than-normal values (SGO-T: 69 U/l and SGP-T: 73 U/I). IgA results were normal for all patients. Finally, the ATA of two patents were higher-than-normal values (62.7 ng/ml and 63.5 UI/m) (Table 1). One of them with a recent CD diagnosis and the second one was in recovery from an infectious condition.

When associating the plasma 25(OH)D concentrations with the nutritional status of the patients, insufficient and deficient parameters were found in nine celiac patients with a normal nutritional status, two with overweight and one with obesity, representing 75% of the studied children and adolescents (Figure 1). The higher deficit was found in the normal nutritional status. These results had no statistical significance.

Associations were made between the plasma 25(OH)D concentrations with the BMI classification, gender, height classification, FM%, AMC, AFA, AMA, and tricipital skinfold classification, where no statistically significant difference was found as well as in the associations between plasma 25(OH)D concentration with age, age of diagnosis, evolution time, height and BMI z-score, SGP-T, hemoglobin, hematocrit, IgA, ATA, FM%, and tricipital skinfold.

Discussion

Most of the studied group had an adequate control of the CD management, which was reflected in the ATA levels and the normal nutritional status, except for five patients with malnutrition by excess, four with overweight, and one with obesity. When comparing this with national data, we can observe that our sample showed lower figures of malnutrition by excess than the rest of the healthy Chilean child population[19].

In a retrospective study of 390 Israeli children recently diagnosed, with an average age of 7.1 years, an 11.8% overweight and 5.6% obesity prevalence was reported[20]. In line with these results, the CD pediatric population in Western countries shows a malnutrition prevalence between 8% and 40%[21]. The coexistence of CD and obesity has been explained by the compensation theory, according to this hypothesis, those nutrients that cannot be absorbed due to the villi atrophy in the proximal small intestine is compensated by the increase in the absorption capacity of the distal small intestine. Therefore, these patients not only do not lose weight but could present overweight or obesity. In addition, it is well documented that the fat absorption coefficient remains static, thus, children with a high-energy intake can develop overweight or obesity[20,22].

In our study, a higher incidence of short stature and low normal height was observed (43.7%), similar to the results reported in the recent study of 530 Finnish children, where 182 (34%) of children with CD had short stature, however, it is important to note that the definition of short stature was different from the one used in our study[23]. The most common extra-intestinal manifestation in CD children is the short stature, although this association is not yet clear[24,25]. Traditionally, it has been attributed to malnutrition, but other authors describe a growth hormone (GH) dysfunction in CD children. Reduced GH levels induce lower IGF-1 concentration, which may contribute to the IGF deregulation in CD children[24]. Some authors propose that there could be two different physiopathological mechanisms for low height. On one hand, in children with classic symptomatology the cause would be malabsorption, and on the other hand, in those with non-classic presentation would be due to abnormalities in the IGF-1 GH axis[23]. Others describe that a late diagnosis, after the fourth year of age, is the most likely cause of this finding[26]. In contrast, the recent study of Finnish children showed that short stature in symptomatic children with CD would be associated with younger age and severe presentation at diagnosis[23].

In this study, the plasma 25(OH)D concentrations in blood were insufficient (20-29 ng/ml) and deficient (< 20 ng/ml) in 75% of the sample, which corresponds to 12 patients. Considering both insufficient and deficient concentrations, in the Canadian study of 43 children and adolescents (3-17 years), 43% of the sample showed 25(OH)D concentrations lower than 30ng/ml at the moment of diagnosis[27], being lower than our study. In the case of only deficiency, four patients (25%) had it, which was different from the Erdem study[4], where 50% of 52 pediatric patients from Turkey recently diagnosed with CD, showed 25(OH)D deficiency, reported as a 25(OH)D deficiency (< 20 mg/dL). In line with what was reported in the only Chilean study published in 2003, only five (20%) out of the 25 studied celiac children and adolescents had 25(OH)D concentrations lower than 15 ng/ml[9], emphasizing that the insufficient cut-off point of this study was lower. In the Villanueva study[8], in a retrospective sample of 24 American children with CD (3-12 years) who, when comparing them with a control group, had no differences in the plasma 25(OH)D concentrations when sorting by BMI. Consistent with these findings, the Lerner et al. study carried out with Spanish and Israeli children and adults, no 25(OH)D deficiencies were found. These authors stated that the possible causes of sufficiency were due to a higher consumption of dairy products and vit D-fortified foods. In addition, they received routinely vit D supplements during the first year of life and had a higher sun exposure and a greater adherence to a gluten-free diet[1]. It is important to emphasize that the main factors that can increase the vitD deficit risk are the geographic location and higher altitude, in the case of Concepción, which is located at 36º south latitude, which is the recognized limit of higher vit D deficiency risk. Other factors are older age, winter, dark skin, lower sun exposure, the use of sun protection factor, unhealthy eating habits, and low intake of vit D-fortified foods. It is important to note that there are no public policies of vit D food fortification in Chile.

When associating the plasma 25(OH)D concentration with the nutritional status in our study, the insufficient and deficient parameter were concentrated in the group with normal nutritional status (nine cases, 56.2%). However, no statistically significant differences were found, contrary to what was reported in the Villanueva study, where CD children with obesity showed lower 25(OH)D concentrations, compared with eutrophic children (8). These findings are consistent with other studies that report that the higher obesity prevalence, the lower the 25(OH)D concentrations compared to healthy, non-obese children. On the one hand, it is suggested the excess of body fat increases the vit D sequestration and, on the other hand, a lower sun exposure due to sedentism and unhealthy diet in patients with obesity[8,28]. It is probable that in the studied group, most of them eutrophic, the possible use of permanent photoprotection and seasons influenced the 25(OH)D concentrations.

When comparing our results of plasma 25(OH)D concentrations with a recent study of 426 healthy school children that live in Santiago, Chile, we found that 39.7% of the sample had suboptimal 25(OH)D values (< 30 ng/ml), which is much less than the 75% observed in our study[29].

One of the limitations of our study is the sample size and the exclusive residence in Concepción. In addition, there was no control group to allow for further analysis.

In conclusion, deficient and insufficient plasma 25(OH)D concentrations are frequent in the group of Chilean children and adolescents with CD, possibly influenced by the geographic area, malabsorptive diseases, and not having public policies that favor the fortification of food with vit D in the regular diet.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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