Vitamin D Metabolism in Celiac Disease

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Celiac disease is a chronic autoimmune disorder involving the small intestine, characterized by villous atrophy, crypt hyperplasia and an increase in intraepithelial lymphocytes. Due to both calcium malabsorption and immune activation, a high prevalence of bone mass derangement is evident in this condition, regardless of the presence of overt malabsorption. In untreated patients, secondary hyperparathyroidism is responsible for the hyperconversion of 25-vitamin D into 1,25-vitamin D making mandatory the determination of serum levels of both vitamin metabolites to avoid a wrong diagnosis of vitamin D deficit. A gluten-free diet allows for a normalization of bone and mineral metabolism, reverting these abnormalities and raising some doubts on the need for vitamin supplementation in all the patients.

Keywords: celiac disease ; gluten-free diet ; vitamin D

1. Introduction

Celiac disease (CD) is a chronic autoimmune disorder of the small intestine caused by the intake of gluten in genetically predisposed subjects. The gluten-evoked immune response alters enteric mucosa architecture, determining villous atrophy, crypt hyperplasia and an increased number of intraepithelial lymphocytes [1]. Mucosal lesions compromise the absorbing capacity due to a reduction in intestinal surface area and cause, among others, calcium malabsorption and vitamin D metabolism alterations [2][3]. Together with the persistent inflammation [4], intestinal malabsorption is considered a pivotal mechanism for bone mass and mineral metabolism impairment. The impairment of calcium absorption and the consequent endocrine alterations of the secretion of parathyroid hormone and vitamin D metabolism deeply modify bone homeostasis, causing an increased bone resorption stimulating bone turnover.

2. Supplement Vitamin D in CD Patients?

There are many concerns about nutritional supplementation in CD patients, and guidelines are frequently characterized by substantial differences. A recent Consensus Conference underlined the need for further studies aimed at the clarification of the role of vitamin D in the pathophysiology of CD and the need for supplementation [5]. The case of vitamin D is, however, not isolated, as the same considerations could be expressed for calcium supplementation. A correct intake of calcium for the maintenance of optimal bone health and a balance of mineral metabolism depends on the age of the subjects. Adolescents and old subjects need a high amount of calcium due to the rapid growth and the reduced intestinal calcium absorption capacity, respectively. However, the Food and Agriculture Organization (FAO) recommends a calcium intake of 800–1000 mg/day in men and women over 50 years of age [6]. The Institute of Medicine of the United States National Academy of Sciences suggests 1000 mg for 19–50-year-old women and 19–70-year-old men and 1200 mg/day for postmenopausal women and men over 70 years old [7]. The increase in calcium supplementation to over 1200 mg/day may predispose one to an increased risk of urinary stones, but the risk of this complication should be monitored in all the subjects following a pharmacological calcium supplementation.

Serum levels of 25-vitamin D below the value of 30 nmol/L are considered correlated to an increased risk of bone derangement, and values higher than 50 nmol/L or 20 ng/mL are considered appropriate for bone health [8][9][10][11]. A lack of standardization is, however, evident for vitamin D measurement, and comparisons between methods have reported discrepancies of immunoassays in comparison with LC-MS/MS methods [12]. This is still an unmet need hampering clinical research: all the efforts to overcome this impasse are welcome.

An appropriate vitamin D supplementation should consider age and gender, but also skin type, season and geographic area. The USA Institute of Medicine and the European Food Safety Authority (EFSA) agreed to consider 15 microg of vitamin D as a recommended dietary allowance (RDA) [6][12]. In particular, expressed in IU/day, an RDA of 600 IU/day is suggested for adults in the age range of 50–70 years and 800 IU/day is suggested for adults aged >70 years. The goal of vitamin D supplementation should be the achievement of serum 25 vitamin D levels of 50 nmol/L, an effective value for bone health maintenance in more than 97% of North America's people [13][14].

3. Vitamin D Supplementation in Untreated CD Patients

As far as CD patients are concerned, the increased conversion of 25-vitamin D into 1,25-vitamin D is a crucial point and should be particularly stressed. In untreated CD patients, low levels of 25-vitamin D should not be necessarily interpreted as the expression of vitamin deficiency: the hyperconversion to 1,25-vitamin D, secondary to hyperparathyroidism, is the cause of low 25-vitamin D. Consequently, 25-vitamin D supplementation in CD patients at diagnosis could not only result in a useless therapeutic measure, but even in a dangerous treatment, as excessively elevated serum levels of 1,25-vitamin D are characterized by a proresorptive effect, as they enhance bone loss [15].

The indication of vitamin D supplementation in untreated adult CD patients should arise from the evaluation of circulating levels of both vitamin D metabolites, together with the measurement of PTH levels. Low levels of 25-vitamin D associated with high levels of 1,25-vitamin D and PTH should be not approached with supplementation of drugs aimed at the increase in 25-vitamin D, as this measure may enhance the already-stimulated hyperconversion to 1,25-vitamin D and may increase the risk of 1,25-vitamin D-mediated bone resorption. Moreover, it was clearly shown that 25-vitamin D supplementation as an add-on therapy to GFD does not improve bone mass gain in comparison with GFD alone [16], making this therapeutic measure even more useless.

On the contrary, two different approaches could be suggested. Due to the rapid reversal of GFD-mediated modification of vitamin D metabolite levels [16], a conservative approach is justified, associated with a re-evaluation of serum levels of 25-vitamin D, 1,25-vitamin D and PTH after 3 months of GFD [17], to check for the positive effect of the diet.

An alternative approach deduces its rationale on the presence of calcium balance impairment. In untreated CD, the modification of vitamin D and PTH serum levels is the expression of the impaired calcium balance independently from the actual detection of hypocalcemia. Accordingly, oral supplementation of calcium could represent a useful, preliminary therapeutic approach. Villous atrophy may hamper the efficacy of this measure, as untreated CD patients show a reduced calcium absorption, which improves on GFD [18]. However, the description of a rapid improvement of serum levels of both 25-vitamin D and 1,25-vitamin D after three months of GFD [16] suggests that the effect of calcium supplementation on the improvement of secondary hyperparathyroidism is low at the beginning of GFD. Instead, the effect could be evident within the third month of the diet. Moreover, the presence of normal levels of vitamin D and PTH during calcium and vitamin D supplementation begun before diagnosis in untreated CD patients suggests a positive effect of this therapeutic measure, besides the presence of villous atrophy [19].

4. Vitamin D Supplementation in Treated CD Patients

In patients with treated CD, the need for vitamin D supplementation seems less urgent, especially in those patients showing a progressive normalization of biomarkers of calcium balance after the beginning of GFD. If patients follow a strict GFD, it is very improbable that alterations of calcium balance may originate from mechanisms related to gluten toxicity. However, recently, nutritional and biochemical parameters of a group of CD patients on GFD recruited through a patient's association were compared to a group of non-celiac adult volunteers [20]. In both the studied groups, vitamin D intake did not reach the recommended intake, and similar results were obtained for energy, folates, calcium, iodine, zinc and magnesium. In particular, a very low vitamin D intake was reported-around 22% of the recommended intake- in both CD and non-CD subjects, without differences between males and females. Plasma levels of vitamin D were found between 10 and 30 ng/mL in 35% of CD patients. These results were not different when compared to the control group. These results strengthen the need for the measurement of circulating levels of vitamin D, in order both to select patients with vitamin D deficiency and to address them to a nutritional intake evaluation.

The age of the patients becomes crucial: a correct suggestion should consider how menopause age is drawing closer. In patients younger than 45 years, before the perimenopausal period, the persistence of vitamin D deficiency or its recurrence should be investigated towards, first of all, the identification of incorrect adherence to GFD, and secondly, the identification of other conditions responsible for this alteration.

Under this light, one of the main actors of this coexisting alteration is represented by a thyroid disorder [21], which is very frequently associated to CD. In patients with Hashimoto's thyroiditis and Grave's disease, reduced levels of vitamin D were shown [10][22]. Vitamin D deficiency is considered to be responsible for the impaired T-cell suppression causing the release of proinflammatory cytokines and the consequent inflammatory-related alteration of thyroid structure, and therefore, function [23]. Many immune cells, such as macrophages, lymphocytes and dendritic cells, express vitamin D receptors and may convert 25-vitamin D into 1,25-vitamin D [24], which inhibits Th1 cell proliferation and Th1 cell cytokine production and decreases HLA class II antigen surface expression and B cell apoptosis [22][24][25][26]. Oral supplementation

of 2000 IU/day vitamin D (more than twofold higher than RDA) is associated with a reduction in antithyroid autoantibodies suggesting a protective effect [27]. Moreover, it should be emphasized that in CD patients, intestinal malabsorption frequently causes iron deficiency, worsening thyroid function due to the impairment of heme-dependent TPO [28].

Another condition to rule out, if alterations of calcium balance are not dependent on gluten toxicity, is sarcoidosis [29]. It was recently reported by a systematic review and meta-analysis that the risk of sarcoidosis in CD patients is higher than subjects without CD with a pooled OR higher than 7 [30].

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