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UPDATE ON NUTRITIONAL ASPECTS OF GLUTEN-FREE DIET IN CELIAC PATIENTS

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ABSTRACT

A strict gluten-free diet is the only currently available therapeutic treatment for patients with celiac disease, an autoimmune disorder of the small intestine associated with a permanent intolerance to gluten proteins. In recent years, the dramatically prompted changes in the dietary habit of an increasingly large population (celiac disease, non-celiac gluten sensitivity and gluten allergy) has resulted in rising demands for gluten-free products. Before starting gluten-free diet, alteration in intestinal absorption capacity of celiac patients involves deficiencies of nutrients, vitamins and dietary minerals. The habitual poor gluten-free food choices in addition to inherent deficiencies in the gluten-free diet of diagnosed celiac patients may relate with dietary inadequacies. Therefore dietary assessment and counseling at the time of celiac disease diagnosis and ongoing care are crucial as well as fortification of gluten-free foods also need to be considered. This article reviews the nutritional aspects of gluten-free diet in celiac patients and provides an up-date of dietetic recommendations to correct these deficiencies and to ensure optimum gluten-free diet compliance.

Keywords: Celiac disease, Gluten-free diet, Gluten-free cereals, Foodstuffs.

Contribution/ Originality

This study documents the nutritional aspects of gluten-free diet in celiac patients, with special highlight on the assessment of the nutritional status of the patient prior to withdrawal of gluten from the diet.

1. INTRODUCTION

Celiac disease (CD) is an immune-mediated systematic disorder triggered by ingestion of gluten or related prolamins in genetically susceptible individuals [1, 2]. CD is strongly associated with particular HLA genotypes, as only individuals carrying the DQA1*0501 and DQB1*0201 (DQ2), or DQA1*0301 and DQB1*0302 (DQ8) alleles develop the disease. The global prevalence

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of CD is estimated at 1% of the general population although this percentage is probably an underestimation since the condition often being left undiagnosed [3-6].

The most accepted model for explaining the immunopathogenesis of CD is the two-signal model, characterized by a first innate immune response and a subsequent secondary adaptive response, which will promote a histological lesion characterized by a massive intraepithelial infiltration of lymphocytes, crypt hyperplasia and villous atrophy [5].

In a classical CD the ingestion of gluten proteins leads to the inflammation, atrophy, and hyperplasia of the small-intestinal crypts of the patients. However, in a silent CD this disease not only affects the gut, but it is characterized by atypical systemic disease that may cause injury to the skin, liver, joints, brain, heart, and other organs [7]. The presentation and clinical manifestations of CD have changed over the time. In recent years, gastrointestinal symptoms, such as diarrhea or malabsorption, have progressively decreased as the mode of CD onset among both adults and children, whereas nonspecific signs and the atypical manifestations have increased [2, 8].

2. NUTRITIONAL IMPLICATIONS AND TREATMENT OF CELIAC DISEASE: THE GLUTEN-FREE DIET

To date, the corner-stone of CD management is exclusion of gluten from the diet [9]. For most patients, CD goes in remission when they adhere to a strict gluten-free diet (GFD), and they relapse when gluten is reintroduced into the diet [5, 10]. A strict diet is critical to reduce morbidity and mortality [11, 12]. Despite its relevance, maintaining a GFD has a clear impact in the quality of life of CD patients since it is very hard to compatibilize with an active social life due to gluten is a very common food additive. According to several reports, up to 50% of subjects do not comply properly with the diet (either voluntary or involuntary) and will develop an active symptomatology which may even facilitate the development of the expensive and difficult to treat refractory CD [5, 13].

Although official data are lacking, the number of patients embracing a GFD is rapidly growing as well as a global market of gluten-free (GF) products [14]. Not only people with gluten intolerance consume GFD, certain people think that these products are healthier than conventional products or feel they are helpful for weight loss programmes. The GFD is based on 2 fundamental premises: (1) the elimination of all products containing wheat, barley, spelt, rye, and certain varieties of oat, and (2) the elimination of any products deriving from these cereals (starch, flour, semolina, bread, pasta, pastries, and cakes) and of all the products of these grains in food products, beverages, and medication [15-17].

Between 70-95% of patients with CD show rapid clinical improvement with the disappearance of symptoms 2 weeks after GFD [18-20]. Despite celiac patients start to gain weight and feel better, they should be advised not to consume gluten, because as even small amounts of gluten can lead to mucosal alterations [17].

Before starting the GFD patients may have certain nutrient deficiencies that may require correction through supplementation until the optimum absorption capacity of the intestine has been completely restored [21]. The GFD should meet an individual´s nutrition needs and involve a balanced diet containing optimum macronutrients and micronutrients. The relative deficiency of lactase present in about 30% to 60% of newly diagnosed cases of CD makes necessary to limit the consumption of lactose at the beginning of GFD [17]. Some studies [22, 23] have found that limiting the intake of carbohydrates in celiac patients results in an increase of fat consumption and therefore, 30% of all patients are overweight and 50% suffer from constipation.

Anemia has frequently been reported as the most frequent extra-intestinal symptom of CD [24-26]. Reduced levels of iron, folate, vitamin B12, vitamin D, zinc, and magnesium are common in untreated CD patients, probably due to loss of brush border proteins and enzymes needed for the absorption of these nutrients [27]. Moreover, dietary inadequacies in CD patients are common and may relate to the habitual nutritional poor choices in addition to inherent deficiencies in the GFD. Therefore, could be useful monitoring the nutrients level through patients´ blood tests, before and after the GFD, to achieve an efficient and complete recovery.

2.1. Iron Deficiency Anemia

Iron is absorbed in the proximal small intestine and the absorption is dependent upon several factors, including an intact mucosal surface and intestinal acidity [28, 29]. Iron deficiency anemia (IDA) occurs very frequently in CD patients because iron absorption site is most severely affected by CD. Halfdanarson and coworkers [28] reported the prevalence of IDA in up to 46% of patients with subclinical CD, and its prevalence was higher in adults than in children. Similarly, in a population screening, 50% of young or middle-aged adults were identified with anemia [30]. In an additional study [31], consisting predominantly of young females, anemia was encountered in 28% of celiac patients, being the most common extraintestinal finding.

Once gluten is excluded from the diet, ferropenia can persist until the morphology of the intestine be restored and iron stores replenished [32-34]. Another aspect that contributes to iron deficiency in CD patients is that GF products tend, generally, provide lower amounts of iron and not be fortified [35-37]. Therefore, iron supplements are usually prescribed, mainly, to supply this deficiency of iron in the cereals [38]. The consumption of iron source foods and calcium supplements should not be done at the same time because their interaction which contribute to decrease the iron absorption [39]. A characteristic feature of IDA associated with CD is its refractoriness to oral iron treatment. There are conditions which oral iron is poorly tolerated or ineffective in celiac disease such as inability to absorb iron optimally or gastrointestinal side effects [29].

2.2. Vitamin B12 Deficiency

The main site of vitamin B12 absorption is the distal ileum, where it is absorbed bound to intrinsic factor, however, a small proportion is also absorbed passively along the entire small bowel [40]. Therefore, deficiency of vitamin B12 is common in CD, ranging 8-41% and frequently results in anemia [41-43]. In most cases, vitamin B12 concentration normalizes once patients start the GFD, but symptomatic patients may require supplementation to improve subjective health status [27, 41]. In celiac patients, monitoring concentrations of vitamin B12 should be measured routinely by using the Schilling test that checks vitamin B12 absorption and evaluates the presence of pernicious anemia [41, 44]. The classic treatment of cobalamin deficiency is by parenteral administration of the B12 vitamin. However, recent data has been supported the efficacy of oral cobalamin therapy [45].

2.3. Vitamin D and Calcium Deficiency

There are two ways of acquiring vitamin D, either cutaneous irradiation or by diet. Dietary vitamin D is absorbed through the small intestine (predominantly in the proximal portion) [46]. Vitamin D is an essential prohormone, primarily responsible for calcium homeostasis, though it has additional functions that go beyond bone metabolism. Calcium absorption is decreased in CD as a result of decreased vitamin D levels and the underlying inflammatory process resulting in compensatory secondary hyperparathyroidism [47].

Different studies have based on vitamin D and calcium deficiency in CD patients. Almost 60% of patients with CD were found to be vitamin D deficient or insufficient [48, 49]. Despite early bone disease is frequent in CD due to, firstly, as a result of malabsorption of vitamin D and calcium and second, because of frequent lactose intolerance prior to CD diagnosis make that patients eliminate milks products from their diet, osteoporosis and osteomalacia have been reported a prevalence of 26% and 20%, respectively [48, 50]. Fortunately, GFD treatment can resolve vitamin D deficiency and derived osteoporosis in most celiac patients [48].

2.4. Folate Deficiency

Folic acid is an essential element of amino acid and nucleic acid metabolism and metabolic regulation, required for normal hematopoiesis and development of the nervous system [51]. Folate is absorbed primarily by the proximal small intestine (jejunum) and therefore, malabsorption is frequent in the small intestine diseases [51, 52]. The diagnosis of folate deficiency is usually made by measuring serum folate and red-cell folate levels. Serum folate levels tend to be increased in patients with vitamin B12 deficiency, presumably because of impairment of the methionine synthase pathway and accumulation of methyltetrahydrofolate, the principal form of folate in the serum [53]. Previous studies have shown that many untreated CD patients are folate deficient [24, 54]. Two small studies found that folate deficiency is a common finding in children but it does not usually result in anemia [55, 56]. More-recent studies have confirmed

that folic-acid deficiency continues to be a frequent finding in subjects with newly diagnosed CD and even in adolescents and young adults with CD detected by screening [30, 57, 58].

2.5. Other Micronutrients and Mineral Deficiencies

Patients with CD have been reported to be deficient in various micronutrients necessary for normal hematopoiesis such as vitamin B6, copper, selenium, and zinc [59]. Copper deficiency has been described in association with CD. Copper levels normalize within a month of adequate supplementation and a GFD although reversibility of established neurological manifestations is unclear [42]. Deficiencies in vitamin B6, pantothenic acid, and riboflavin have also been suggested as etiologic factors in patients with CD but recent data are lacking [24]. However, universal analytical detection and supplementation of these micronutrients and minerals are not recommended because these deficiencies reversed rapidly once patients start following GFD [17].

3. RECENT ADVANCES ON GLUTEN-FREE CEREALS AND FOODSTUFFS

In recent years there has been rising demands for GF foodstuffs parallels the apparent or real increase in CD, non-celiac gluten sensitivity and gluten allergy [14]. The global GF product market is growing at a compounded annual growth rate of 10.2% by 2018 [2].

From a nutritional point of view, gluten exclusion does not entail particular problems because it is a mixture of proteins with low nutritional and biological value. However, GFD creates huge limitations, especially in social activities related to food [60]. The gluten technological characteristics, like extensibility, resistance to stretch, and gas holding ability, favor its use in many food products [61]. The high technological value renders gluten almost indispensable in baked products, and its replacement, as structure-building protein, presents a major technological challenge for the food industry. Although many advances have been made in the preparation processes of GF products, using starches, hydrocolloids, gums and novel ingredients [62], many GF industrial products available on the market exhibit a low nutritional quality, poor mouth feel or flavor [63] and, no less important, are particularly expensive. To solve these issues, different studies [60, 64, 65] have been devoted to the use of *in vitro* detoxified flour by microbial enzymes or flour from ancient wheat cultivars, in the formulation of pasta and baked goods.

Non-gluten-containing sources available in product formulation include cereals (rice, corn and sorghum), minor cereals (fonio, teff, millet and job's tears), pseudocereals (buckwheat, quinoa and amaranth) and other cereals. Some of these grains are nutrient-dense and could improve the nutritional quality of GFD and GF products. As the environmental conditions for growing these grains are variable, availability of regular supplies is not always assured [14]. Although the application of pseudocereal flours as GF ingredients is increasing, the commercial production of pseudocereal-containing GF products is limited, and only a small number of products containing these flours are available. Cereal based GF products can be rich in carbohydrates and fats, and

they have deficiencies in macro and micronutrients like vitamins B and D, calcium, iron, zinc, and magnesium, as well as fiber [66-68]. Therefore, GF cereals do not contain the same nutritional content as their gluten counterparts [35, 69]. Different proteins have been proposed as alternative for both playing the polymer role and increasing the nutritional value of GF products. The incorporation of other ingredients/nutrients like omega-3 lipids, specific proteins, etc. is a choice to improve the nutritional composition of GF products [14]. GF food prepared with corn and rice starch has a high glycemic index [70, 71] and increases the risk to develop metabolic syndromes in CD patients [72, 73].

4. NUTRITIONAL IMPACT OF GLUTEN-FREE DIET (GFD) IN CELIAC PATIENTS

The nutritional status of celiac patients in the past was severely compromised as a result of late diagnosis and because only the cases in which the intestine was significantly affected were diagnosed [17]. Today, the nutrition status at diagnosis depends on the time the disease is active and has not been treated, the extent of the intestinal damage, and the degree of malabsorption [17]. The GFD should meet an individual´s nutrition needs, based on age, gender, and physical activity and, involving a balanced, rational, varied, pleasant and sufficient diet. The most accepted distribution of nutrients establishes that the carbohydrate intake should represent 50-60% of the diet´s total energy value, fats should amount to between 30-35% and proteins should contribute approximately 10-15% [74].

Historically, counseling for CD has focused on the absence of gluten in GF foods; however the nutritional quality of GF foodstuffs is an important aspect to consider [75]. The quality of the GF products available on the market, and food choices, may represent major determinants in the deficiencies in macronutrients and micronutrients of celiac patients [76].

Several studies have confirmed the theory that there is great nutritional variability between GF products and their gluten-containing counterparts [2, 75]. The imbalance nutrient intake of celiac patients is attributable to the nutritional composition of specific foods without gluten [77]. Nutritional studies with CD patients on GFD with cereal based GF food revealed nutrient deficiencies, particularly of vitamins and minerals, as well as an increased of obesity risk [61]. GFD has been described as excessive in fat and protein and low in carbohydrates and fiber [78, 79], determining factors in cardiovascular disease risk factors [22, 23].

5. CONCLUSION

Currently, the only treatment available for CD individuals is a strict life-long GFD. Nevertheless, it is well known that compliance to GFD is cumbersome, costly and incompatible with an active social life since gluten is present as a common food additive. The intestinal lesion caused in untreated CD patients leads to various deficiencies of nutrients, vitamins and dietary minerals. Monitoring the nutrients before and after the GFD is essential to achieve an efficient

and complete recovery. Several practical measures such as those reviewed in this article should be taken to evaluate the nutrition status at diagnosis.

Inadequacies in macronutrients and micronutrients of CD patients are common and may relate to the quality of available GF food choices. The replacement of the unique technological properties of wheat gluten represents the major task of industry for providing high quality GF foods in terms of structure, loss of starch during cooking, and optimal cooking time. Different alternatives have been proposed to offer celiac patients other alternatives to diet therapy.

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