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Nutritional profile of adult patients with celiac disease

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Abstract. – Celiac disease (CD) is a chronic immune-mediated gluten dependent enteropathy induced by ingestion of gluten, characterized by intestinal malabsorption and subtotals or total atrophy of intestinal villi. The predominant consequence of CD in untreated patients, is malnutrition as a result of malabsorption. Moreover, several and increasing extra-intestinal clinical manifestations have been described in the CD patients. Strict adherence to a gluten-free diet (GFD) improves nutritional status, inducing an increase in fat and bone compartments, but does not completely normalize body composition and nutritional deficiencies. An early and accurate evaluation of nutritional status can be of the pivotal step in the clinical management of the adult CD patients. The aim of this review is to present the most important and recent data on nutritional and metabolic features in the CD adult patients, the related implications and the effects of the GFD on these conditions.

Key Words:
Celiac disease, Gluten-free diet, Nutritional status, Body composition, Metabolism.

Abbrevations

CD = celiac disease; GFD = gluten-free diet; T1DM = type 1 diabetes mellitus; FM = fat mass; FFM: fat-free mass; DXA = x-ray absorptiometry; BMI = body mass index; Apo-A1 = apolipoprotein A1; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein cholesterol; NAFLD = non-alcoholic fatty liver disease; SIBO = small intestinal bacterial overgrowth; HLA = human leucocyte antigen.

Introduction

Celiac disease (CD) is a chronic, immune-mediated enteropathy of the small intestines, induced by dietary gluten in genetically pre-disposed individuals. It is characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi, which improves after gluten-free diet (GFD)[1]. Gluten is a general term for insoluble prolamine polypeptides found in wheat (gliadins and glutenins), rye (secalin), barley (hordein) and other closely-related grains[2]. Unlike wheat, rye and barley, oats have been shown to be non-immunogenic in most individuals with CD[3]. In genetically predisposed individuals, gluten ingestion generates an inflammatory reaction predominantly located in the jejunum. Gluten-induced small intestinal mucosa injury will eventually reduce the intestinal absorptive area and interfere with the uptake of micronutrients[1,4]. The prevalence of CD in the general population is reported to be around 1%[5,6].

CD can be diagnosed in childhood with classical symptoms, such as diarrhea and malabsorption, but also later in the adults evidenced with a wider spectrum of symptoms than in children[4]. Approximately 50% of adult patients do not have significant diarrhea, but only show weight loss and nutritional deficiencies with a consequent iron deficiency or macrocytic anemia, due to folate, calcium, vitamin D and vitamin K deficiencies[5,6]. It has been reported that the strict adherence to a GFD improves nutritional status[7]. In addition, the changes in nutritional profile may help the clinicians to detect an incomplete adherence to GFD[7-9]. Thus, an early identification of nutritional deficiencies may have a pivotal role in preventing malnutrition related complications and improving the quality of life of CD patients[10,11]. Moreover, several and increasing extra-intestinal clinical manifestations have been described in the CD patients, such as infertility,

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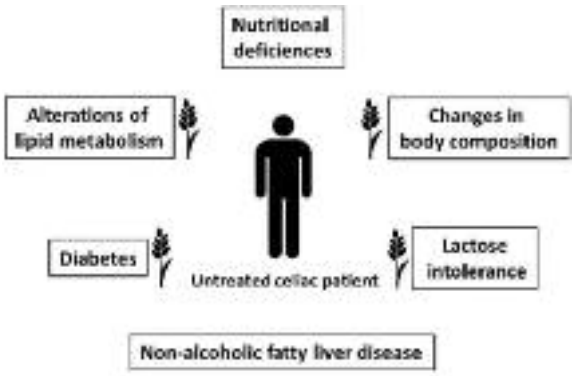

Figure 1. Abnormal septum in the left atrium shown by apical four-chamber view.

neurologic, and psychiatric syndromes, skin manifestations, bone fractures, and autoimmune diseases, including type 1 diabetes mellitus (T1DM), thyroid and/or liver diseases[12].

The aim of the present review is to present the most important and recent data on nutritional and metabolic features in the CD adult patients, the related implications and the effects of the GFD on these conditions.

Clinical and nutritional features

Untreated patients affected by the classic form of CD, characterized by diarrhea, and weight loss, are at high risk of malnutrition subsequent to nutrient malabsorption related to small intestinal atrophy (Figure 1). Often as a result, the CD patients generally lack energy and strength that can create abnormal conditions described as chronic fatigue[13]. Gislason[14] states "As a general rule, celiac and many other gluten-sensitive patients have nutrient deficiencies until proven otherwise".

CD treatment consists of a lifelong treatment with a GFD, which can drastically improve or restore the intestinal mucosa and decrease the risk of morbidity and mortality. The digestive and absorptive processes in CD patients may be compromised consequently to an increase in inflammatory signaling molecules[1,4].

Several studies have shown that nutritional deficiencies are common in subjects with active CD, and occur during silent or subclinical stages as well, and therefore, should be screened and evaluated in CD patients[15]. In particular, vitamin deficiencies may aggravate retinopathy (vitamin A), systemic and peripheral neuropathy (vitamins B12 and E), complications of pregnancy (iron and folic acid deficiency), dental disease, osteopenia, and osteoporosis (vitamin D). Deficient intake and absorption of calcium and vitamin D, and the development of secondary hyperparathyroidism should be present in the patients with osteoporosis, and several studies have shown that osteopenia occurs in adult CD patients and that a GFD can improve bone mineral density[16,17]. As far as the hydrosoluble vitamin deficiencies, the involved CD patients following a GFD presented poorer vitamin status for folate and vitamins B6 and B12, even when taking the prescribed nutrient supplements. Although vitamin B12 deficiency is not unusual in CD, pernicious anemia is considered uncommon, while recovery from iron-deficiency anemia is possible with a GFD alone[16,18]. However, the degree of recovery due to the nutrients malabsorption is dependent on age at onset, extent and duration of the condition and other concomitant health factors[19].

Treatment with life-long GFD causes a marked improvement or a complete restoration of the intestinal mucosa, while the literature suggests that the nutritional deficiencies do not completely normalize after GFD[15,20]. Consequently, an early identification of nutritional deficiencies may have a crucial role in preventing malnutrition-related complications and in improving the quality of life of the patients[21].

Moreover, CD may be associated to lactase deficiency, with consequent lactose intolerance. In order to reduce the gastrointestinal symptoms linked to lactose malabsorption, the untreated CD patients often reduce the intake of lactose-containing products that are frequently energy-dense food items. A possible daily caloric impairment could thus take place. It has been shown that lactase deficiency seems to be the only manifestation of CD[22]. Finally, peculiar clinical and nutritional assessment could be present in the CD patients with T1DM. Unexplained hypoglycemia with a reduction in insulin requirements should suggest investigating for an undiagnosed CD[23]. On the other hand, in the CD patients with associated T1DM, an acute hyperglycemia and a steady rise in glycated hemoglobin could occur with the initiation of a GFD, due to intestinal healing and better absorption.

It is our opinion that an adequate replenishment of the nutrients lost to inefficient absorption is essential to minimize the secondary health problems caused by gluten intolerance (Table I).

Body Composition and CD

Patients with the classic form of CD are characterized by weight loss directly connected with malabsorption and subsequent risk of malnutrition[1]. In order to perform a correct evaluation of nutritional and metabolic status, it should be necessary to assess body weight components, i.e. fat mass (FM) and fat-free mass (FFM), total body water and to evaluate energy expenditure and nutrient utilization[24]. Assessment of body composition is pivotal in the clinical management of the CD patients, and can be evaluated by simple and easy-to-perform methods, such as anthropometry, skinfold thickness and biochemical measurements, or by computed tomography and magnetic resonance imaging[25]. These latest are also used to measure central fat mass by using a single scan at the lumbar level. Very expensive techniques for body composition evaluation such as isotopic dilution methods, neutron activation analysis, computed tomography and magnetic resonance imaging, need a well-trained staff and are performed only in highly specialized centers[16,26].

The most commonly used techniques to assess body composition in clinical practice are: anthropometry and skinfold thickness measurement, bioimpedance analysis and dual-energy x-ray absorptiometry (DXA)[27,28]. In particular, determination of body weight, height, body mass index (BMI), computed as the ratio between body weight (Kg) and height (m^2), are very useful tools for anthropometric assessment of the patients. The BMI values between 18.5 and 24.9 kg/m^2 indicate a normal weight condition, while values <18.5 or >24.9 indicate a condition of underweight up to malnutrition or overweight up to severe obesity, respectively. Measurement of waist circumference significantly correlates with an increased risk of developing cardiovascular and metabolic diseases. Body fat and density can also be indirectly determined by skinfold thickness taken at the four standard sites: biceps, triceps, subscapular and sacroiliac.

Bio-impedance analysis is a rapid and simple method for measuring the different body components; it is based on the principle that conductance of a tissue or of the entire body correlates with the mean water and electrolytes content and thus the conductivity is greater in the FFM and proportional to it[27].

DXA is based on the attenuation that an x-ray or a photon ray receives when passing through a human body. The total body densitometer used to measure bone mineral density should be used also to assess the amount of body fat and FFM. DXA is a very precise and reproducible technique for measuring soft tissues and particularly FM[29,30].

As far as the assessment of energy requirements is concerned, the total energy expenditure measured over 24-hours can be determined using sophisticated and expensive techniques, such as the double-labeled water technique and the calorimetric chamber or in clinical practice by portable indirect calorimeters. The total energy expenditure is made of different components, and open-circuit indirect calorimetry is the most commonly used technique to assess resting metabolic rate and diet-induced thermogenesis; this procedure, by means of gaseous exchange and 24-hours urinary nitrogen excretion measurements, allows to determine energy expenditure and substrate utilization, providing the respiratory quotient value, which is computed as the ratio between CO^2 excretion and O^2 production by the patients[31,32].

The literature has shown lower body weights and lower FM and FFM contents in both untreated and treated CD patients than in the control subjects[33,34]. A longitudinal study, showing that the untreated patients of both sexes and treated male patients, had the FFM values that were significantly higher than those of the control subjects. However, there was a significant increase in body weight and FM after the GFD treatment. As a consequence of the larger decrease in FM than in FFM in the CD male patients after the GFD, these patients had very high % FFM values. Moreover, higher resting metabolic rate values were found in both CD groups than in the control subjects[31]. The increased rate of intestinal

Table I. Nutritional advices for celiac patients.

Consume natural gluten-free foods, naturally rich in fibers, iron and folates
Use high-calcium-content food instead of milk and derivates in presence of lactose intolerance
Check gluten free products with low glycemic load
Reduce foods and gluten-free products containing phytic acid
Provide supplementation of minerals and/or vitamins, if necessary
Counselling and psychological support, can improve dietary compliance

mucosa protein synthesis and the renewal and migration of epithelial cells reported in untreated CD could be considered directly linked to the increased resting metabolic rates in these patients, in addition to the inflammatory nature of the disease[35]. The untreated CD patients oxidize more carbohydrates, as shown by the higher the non-protein respiratory quotient value in the untreated patients than in the control subjects and the treated patients, and this aspect is related to the necessity to provide energy to the organism, considering the chronic lipid malabsorption, and it was also demonstrated by the non-different total daily energy intake among the control group and the CD patients, both before and after the GFD treatment[31,36].

Lipid Metabolism and CD

With regard to the lipid metabolism in the CD patients, an alteration in lipid metabolism can occur in disorders of the small gut mucosa, as a consequence of lipid malabsorption and decreased intake[37]. In this pathogenetic link, the presence of low serum concentration of high-density lipoprotein-cholesterol (HDL-C) has been identified as an early sign of CD, and a strong correlation between HDL-C concentration and decreased FM has been shown[38]. This feature could be explained by the reduction in cholesterol-transporting lipoproteins, induced by the decreased lipid absorption and the decreased apolipoprotein (Apo)-A1. The latter is produced at the small intestines level and presents the main portion of HDL-C particles[39]. At the same time, a significant increase in triglycerides, total cholesterol and HDLC, but not in low-density lipoprotein cholesterol (LDL-C), was found in the CD patients after the GFD. Therefore, after the GFD, a significant increase occurs in triglycerides, total cholesterol and HDL-C serum levels, except for the LDL-C, which may be explained by increased Apo-A1 secretion by intestinal cells and increased nutrient absorption with greater body fat storage[40]. The HDL-C levels present one of the most relevant cardiovascular risk factors, and the improvement in the lipid profile after the GFD suggests that it has a protective role in the prevention of cardiovascular disease[34].

Non-alcoholic Fatty Liver Disease and CD

The persistent elevation of transaminase levels is the most common liver abnormality found in the untreated CD patients[41]. Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the general population worldwide[42]. As a consequence, a wide spectrum of liver involvement from simple steatosis and steatohepatitis to cirrhosis and even hepatocellular carcinoma may occur. The etiology of NAFLD has not been defined so far. However, a number of risk factors obesity, diabetes and dyslipidaemia may be associated with NAFLD. In a minority, but a significant number of the patients, CD is not a recognizable risk factor for NAFLD[43]. In the CD patients altered intestinal permeability has been proposed as an etiologic factor in the development of NAFLD. The increased permeability to intraluminal antigens could induce an immune response against the antigens sharing common epitopes to self-liver proteins and/or against the cryptic antigens unmasked by the reaction with gliadin[44,45]. The association between the intestinal increased permeability and the small intestinal bacterial overgrowth (SIBO) may reflect qualitative and quantitative changes in the gut microbiota, which lead to the disruption of the intestinal barrier, the subsequent translocation in gut bacteria, Kupffer cell stimulation, production of pro-inflammatory cytokines and reactive oxygen species with the development of portal endotoxemia and liver damage[43]. An Italian research group reported that NAFLD is associated with increased gut permeability, and that this abnormality is related to the increased prevalence of SIBO in these patients[46]. However, the mechanisms of the intestinal permeability changes include some other factors, acetaldehyde generation from alcohol, nitric oxide production and the alterations in individual nutrients[45].

Obesity and CD

Recent data clearly reported an increased prevalence of obesity among the subjects affected by subclinical or silent CD and almost half of the adult patients with CD had a BMI over 25 Kg/m^2 at diagnosis[46]. The most common clinical presentation of obese CD patients were abdominal pain, diabetes, and diarrhea. The symptoms improved in all the patients on a GFD. The data on a cohort of 371 CD adult patients, evaluated at diagnosis and 2-year after the GFD treatment, investigated the association between the lower BMI and female sex, history of diarrhea, reduced hemoglobin concentration, reduced bone mineral density and higher grades of villous atrophy[18]. The authors reported that 81% of the patients had gained weight on the GFD, including 82% of those initially overweight. In a retrospective

study, Cheng et al[33] evaluated a large sample of adult patients (n=369, 67.2% female), from 1981 to 2007, with a nutritional follow-up over 2-4 years, who did not receive any specific dietary guidelines for weight control. Among the weight, 7.3% of the patients were underweight, 60.7% normal, 15.2% overweight, and 6.8% obese. The women had a higher rate of low BMI than men (21.3% vs. 9.1%) and more men were overweight (23.1% vs. 11.3%). No gender differentiation was made in histology and in clinical presentation. Overall, on the GFD, 54% patients gained weight and 38% lost weight. The CD patients initially underweight, 3.4% became overweight and 1.7% obese; the patients with normal weight, 6.5% became overweight; those overweight 6.3% became obese; and finally among those obese, 5.9% became overweight[33]. The GFD seems to increase the risk of overweight or obesity, especially in those that adhere closely to the GFD. This trend is the consequence of the fact that the majority of gluten-free foods, consumed daily by the CD patients during the GFD have a high glycemic load due to the high content of sugar in glucose syrup and flour derived from rice and potatoes with hydrogenated fats, low fibers, and protein content[47-49]. In particular, an incorrect dietary regimen can be induced by the availability of commercial gluten-free snacks and biscuits with a high content of lipids. Our opinion is that weight maintenance counselling should be an integral part of celiac dietary patient education. A natural GFD, rich in fibers, without any or low added sugar levels, is recommended.

Diabetes mellitus and CD

The association of CD with autoimmune insulin-dependent T1DM is one of the most intensely studied conditions. The diagnosis of the two diseases is often simultaneous or CD subsequent to diabetes[50]. The prevalence of CD among the patients with T1DM has been estimated to be approximately 4%[51]. Conversely, it has been reported that CD is also associated with an increased risk of subsequent T1DM before 20 years-old[52]. In this way, it is clear that a screening for CD is required in the adult diabetic patients. The pathogenetic link is shown by the human leucocyte antigen (HLA) class II risk genotypes. Approximately 90% of the individuals with T1DM present either HLA-DQ2 or DQ8, compared to 40% of the general population[53]. In the patients with both conditions, the GFD performs a better metabolic control of diabetes, although with a slight increase in an insulin dose due to the correction on the intestinal malabsorption and a higher glycemic index of gluten-free products[51]. Furthermore, the GFD has protective effects on the development of vascular complications in the T1DM patients[54]. However, a lower adherence to the GFD and lower quality of life has been reported in the patients with both CD and T1DM. A psychological support can help to increase the GFD compliance in these patients[55].

Nutritional Deficiencies and CD

It is well known that, at time of diagnosis of CD, there are many cases of malnutrition. The most common deficiencies involve vitamin D, calcium, iron, folic acid, and vitamin B12. Up to 70% of CD is significantly associated with reduced bone mineral density[56].

Lactose intolerance, increased in the CD patients, both due to an impaired secretion of trypsin, a pancreatic enzyme that activates the lactase, and to the intestinal villous brush border damage where lactase is located, may have a role in reduced sources of calcium[57]. In addition, impaired secretion of cholecystokinin, which is responsible for absorptive mechanism of fat-soluble vitamins and substances, results in the reduction in vitamin D levels. In untreated CD patients, upper-bowel villous atrophy contributes to vitamin D deficiency. When vitamin D levels are lower or equal to 30 ng/mL, osteoclasts are activated to remove calcium and other minerals from the bone[58]. Moreover, the drugs such as proton pump inhibitors, recommended to the majority of the patients suffering from dyspepsia or reflux disease, reduce calcium absorption, while the limited nutrient digestion, including cow milk proteins, increases the incidence of bone fractures[59].

Iron is absorbed in the proximal small intestines and the absorption depends upon several factors, including an intact mucosal surface and intestinal acidity. Iron deficiency primarily results in the CD patients, with consequent iron-deficiency anemia, for its impaired absorption as a result of the villous atrophy of the intestinal mucosa[60]. However, the CD patients do not often respond well to iron supplementation treatment. Many gluten-free products containing phytic acid (myo-inositol hexakisphosphate) and its salts (phytates) are the main storage form of phosphate in seeds and grains that reduces the bioavailability and chelates certain nutrients, such as iron, calcium, manganese, and zinc, because of its reactive phosphate groups attached to

the inositol ring[61]. The products containing high phytic acid levels are soya-made products, unrefined cereals and legumes, starchy roots, tubers and maize. Single-meal studies of phytate in bran or as sodium phytate have reported that as little as 2 mg phytate can reduce iron absorption by 18%. These studies have also shown that the inhibitory effect increases with the phytate content, such that 250 mg of phytate in a meal can reduce iron absorption by 82%[62,63].

Folate Deficiency is a Common Finding in the CD Patients

The patients affected by CD show low serum/cerebrospinal fluid folic acid concentrations 64. The best folate sources in foods are green, leafy, raw vegetables. Sprouts, fresh fruits, brewer yeast, liver, and kidney also contain high amounts of folates. However, food folate intake cannot be sufficient for the celiac population as folate levels have been found to be low in gluten-free products[65]. Therefore, pharmacologic supplementation should be considered which the best choice is in the patients with CD. Vitamin B12 deficiency is also very common, although it is absorbed in the terminal ileum, free from typical CD mucosal lesions in the CD patients. Deficiency of vitamin B12 is present in 8-41% of the untreated subjects with CD and frequently results in macrocytic anemia[66]. The cause of the vitamin B12 deficiency in CD is not known, but may include decreased gastric acid, bacterial overgrowth, autoimmune gastritis, decreased efficiency of mixing with transfer factors in the intestines, or perhaps, the subtle dysfunction of the distal small intestines[67]. The patients with vitamin B12 deficiency should receive therapy with oral or parenteral vitamin B12 supplementation.

Conclusions

Biochemical components from food must be digested and absorbed properly before they can be utilized by the body. Due to the changes in physiological function in CD, these processes may be challenged and may not normalize completely on a GFD. The derangement in the upper intestinal morphology and alterations in the local chemical environment surrounding the immunological responses to gluten may lead to the increased susceptibility to a variety of metabolic complications. The accurate evaluation of body composition and energy metabolism may be a pivotal step in the management of the adult CD patients. Finally, a correct dietary treatment of the CD patients, not only based on a GFD, may largely improve nutritional status and decrease metabolic complications, improving the quality of life and reducing mortality.

Conflict of Interest

There are no conflicts of interest associated with this work.

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