ABSTRACT: Celiac sprue is a chronic disease, which usually occurs in children and young adults. However, it can develop in any age group, and the prevalence is increasing even in the elderly population. The atypical patterns of clinical presentation in this age group sometimes can cause a delay in diagnosis. Given the lower sensitivity and specificity of serological tests in the aged population, clinical suspect often arises in the presence of complications (autoimmune disorders, fractures, and finally, malignancy) and must be supported by endoscopic and imaging tools. In this review, we highlight the incidence and prevalence of celiac disease in the elderly, the patterns of clinical presentation, diagnosis, and the most frequent complications, with the aim of increasing awareness and reducing the diagnostic delay of celiac disease even in the elderly population.

KEYWORDS: elderly, celiac disease, presentations, cardiovascular risk

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Introduction

Celiac disease (CD) is an immune-mediated enteropathy caused by a reaction to gliadin, a protein fraction contained in wheat and other common grains such as barley and rye. It has been traditionally recognized in children and young adults, although, recently, detection in the elderly population has increased.1,2 Studies report that about 25% of celiac patients were first diagnosed in the seventh decade in several countries, such as Canada, United States, and Northern Europe.3-5

Usually, when onset of CD occurs in adulthood or in elderly, patients can present either with gastrointestinal (GI) symptoms, such as diarrhea, bloating and steatorrhea, or more frequently with weight loss and selective malabsorption of nutrients, such as iron, calcium, and fat-soluble vitamins (A, D, E, and K). Other patterns of clinical presentation, in this age group, can be autoimmune diseases and malignancies, the latter supposed to be related to a longer exposure to the harmful effects of gluten6-9 as compared to other age groups (Table 1).

In this review, we highlight the incidence and prevalence of CD in the elderly, the patterns of clinical presentation, diagnosis, and the most frequent complications, with the aim of increasing awareness and reducing the diagnostic delay of CD even in the elderly people.

Incidence and Prevalence

Nowadays, there is a growing incidence of CD diagnosis among adults, particularly in the elderly.10 The incidence of CD in the age group over 65 years has gradually increased from 4% to 19%–34%.11,12

A large survey conducted in the United States showed that the rate of diagnosis of CD among the elderly (age > 65 years old) was similar to that in the age group 0 to 18 years (16% versus 15%, respectively).13

Currently, the estimated prevalence of CD is about 1% in the general population, although previous data have shown that it was 0.71% around 1990, in the United States,4 which was lower than that in Europe (Italy and Sweden).14-16 Later on, Fasano et al,17 in a multicenter study of serological screening for CD, showed that the occurrence of CD among adults was approximately 1.2%. In addition, authors have also shown that positive seroprevalence for undetected CD in individuals aged between 45 and 76 years was 1.2%. The same epidemiological scenario has been found in a Finnish study, in which the seroprevalence and biopsy-proven diagnosis of CD in persons aged between 52 and 74 years was around 2.1%.18 Another study by Lohi et al demonstrated that CD can be first diagnosed in the elderly population, despite the apparent tolerance of gluten ingestion for the entire life.19

Pathogenesis

Both innate and adaptive abnormal immune responses against gluten in CD patients are caused by pro-inflammatory environment expressed by a massive intraepithelial infiltration and the appearance of the characteristic crypt hyperplasia and villous atrophy,20,21 which leads to the clinical manifestations of the disease. The adaptive immune response mainly acts in the lamina propria of the intestinal mucosa while the innate immune response preferentially involves the epithelial layer.
Dendritic cells (DCs) presenting antigen lead to the outcome (pro-inflammatory or tolerogenic) of antigen-specific immune responses. In addition, DCs promote the maintenance of immune tolerance toward nutrients and commensals, but at due time, they initiate immune responses toward invading pathogens. Following gluten peptide deamination by the enzyme tissue transglutaminase (tTG), DCs submit peptides through the MHC-II molecules, including human leukocyte antigen (HLA)-DQ2 or HLA-DQ8, performing antigen presentation to CD4+ naïve T-cells. Consequently, T-cell response is gluten-specific Th1/Th17 pro-inflammatory T-cells, resulting in a disruption of the oral tolerance to gluten. These T-cells produce a bulk of pro-inflammatory cytokines, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-18, and IL-21, which stimulate other immune cells to the intestine establishing a positive pro-inflammatory feedback that leads to tissue damage. Probably, the first trigger of the mucosal lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure, lesion is the IL-15 production by intraepithelial lymphocytes (IEL) following gluten exposure, which would lead to an increased epithelial permeability indirectly, weakening the tight junctions between the IECs but also directly inducing IEL following gluten exposure.

Patterns of Clinical Presentation

The clinical spectrum of CD is widely variable, from severe and generalized malabsorption with important weight loss to nutritional deficiency of a single nutrient such as iron or calcium, thus configuring the clinical picture of iron deficiency anemia and severe osteopenia or osteoporosis. The reason of which, in the elderly the GI pattern of presentation is less common than in younger adults, is unknown; however, in the aged population, deficiency of micronutrients may often represent the only symptom at presentation.

However, CD occurs more frequently in women as compared with men, with a female to male ratio of 2:1. By contrast, in the elderly, CD is much more diagnosed in men, as compared with women, in whom the incidence increases till the age of 65 years and then starts to decline. GI symptoms, when present in the elderly, are mild, making the diagnosis difficult. Diarrhea, weight loss, and abdominal pain are more commonly indicative of irritable bowel syndrome in the elderly patient than CD. In fact, although CD is the most common cause of steatorrhea in people over 50 years of age, malabsorption is well tolerated in people over 65 years. Diarrhea is mild or intermittent, and occasionally, the elderly celiac patient can present with constipation. In addition, celiac patients could present to a physician with an autoimmune disease, such as hypothyroidism, or with a malignancy, such as lymphoma; in this case, CD might be present without symptoms, as silent celiac disease.

Up to 80% of elderly patients with CD in a British series presented with anemia, mainly due to iron deficiency. However, deficiency of folic acid and vitamin B12 may also be responsible of anemia in these patients, which sometimes can

### Table 1. Differences regarding clinical presentation, serology, histology, associated disease, complications, and response to GFD between young and elderly onset CD.

|                     | YOUNGER CD                      | ELDERLY CD                      |
|---------------------|---------------------------------|---------------------------------|
| Clinical presentation | Anemia, statural growth impairment | Anemia, micronutrients deficiency |
|                     | Diarrhea                        | Constipation, steatorrhea        |
|                     | Weight loss                     | Obesity                         |
| Serology/histology  | High titers                     | Low titres                      |
|                     | Marsh 3                         | Marsh 1–2                       |
| Associated disease  | Type 1 diabetes                 | Osteopenia                      |
|                     | Thyroid disease                 | Neurologic disorders            |
|                     | Migraine                        | Cardiovascular disease          |
| Complications       | Rare                            | Refractory celiac disease       |
|                     |                                 | non-Hodgkin’s lymphoma          |
| Response to GFD     | Fast                            | Slow                            |
| Adherence to GFD    | High adherence                  | Low adherence                   |
be detected through alterations in the peripheral smear.\textsuperscript{45,46} It has been suggested that inflammation may also be the cause of anemia, and in this regard, it has been shown that celiac patients sometimes have raised serum levels of ferritin and erythrocyte sedimentation rate, suggesting a systemic inflammatory state.\textsuperscript{47}

Lack of calcium and vitamin D are consequences of malnutrition, leading to a decrement in bone mass, which contributes to the risk of fractures, especially in elder patients who are already predisposed to bone metabolism disorders.\textsuperscript{48,49} In addition to the above-mentioned clinical problems coming from malabsorption of iron, calcium, and vitamin D, malnutrition can be responsible of hypalbuminemia, which can further lead to hypocalcemia and hypomagnesemia, as well. Peripheral edema and ascites may be clinical signs of reduction in serum albumin. In about 20% of celiac patients, abnormal liver function tests can be present; this condition is already known as “celiac hepatitis”. Peripheral edema, ascites, and hypoalbuminemia associated with alteration of aminotransferases may be responsible for further investigation to exclude a chronic liver disease, but in these patients, gluten-free diet (GFD) has beneficial effects on the resolution of symptoms and regression of liver function test abnormalities.\textsuperscript{48}

In addition to GI symptoms and malabsorption syndrome resulting from bowel involvement, CD can also be diagnosed through associated autoimmune disease and/or complications (Table 2).

One of the most frequent complications of CD is dermatitis herpetiformis, a skin manifestation, characterized by pruritus and papulovesicular eruptions involving the surfaces of elbows, knees, buttocks, and scalp.\textsuperscript{49} Sometimes, it can be the only presentation of gluten intolerance, occurring in about 25% of celiac patients, mostly men, with an age of presentation ranging from 40 to 70 years. The diagnosis is performed by biopsy of the perilesional areas and the subsequent direct immunofluorescence of the sample, showing granular deposition of IgA in the dermal–epidermal junction. GFD is able to resolve the clinical picture even if slowly.\textsuperscript{50–52}

CD can also be associated with mucosal collagen diseases (collagenous colitis),\textsuperscript{53} as well as lymphocytosis of the stomach, colon, and biliary tract.\textsuperscript{54–56} In some patients, collagenous colitis may be the first clue to diagnose CD,\textsuperscript{57} or may present as a complication of CD causing diarrhea apparently refractory, although the patient is on GFD.

Another frequent modality of presentation of CD are autoimmune disorders, sharing with CD association with peculiar HLA haplotypes, occurrence of autoantibodies, multiorgan involvement, and finally dysregulation of immune responses.\textsuperscript{58–61} Knowledge of the risk of an autoimmune disease in celiac patients leads to better management of patients, and some investigators have reported that the risk of developing an autoimmune disease is directly related to the age at diagnosis, as far as the duration of gluten exposure.\textsuperscript{62}

Hashimoto’s thyroiditis and Graves’ disease are the most frequent immune-mediated thyroid disorders affecting celiac elder patients.\textsuperscript{63,64} In the elderly, hypothyroidism has a high prevalence, whereas type 1 diabetes presents a low prevalence.\textsuperscript{65}

Autoimmune liver disease, such as autoimmune hepatitis, biliary cirrhosis, and sclerosing cholangitis, can also affect celiac patients. In these cases, liver involvement is quite different from celiac hepatitis; thus, patients do not benefit from GFD, but from immunosuppressive therapy.\textsuperscript{66}

Neurological complications of CDs are ataxia and neuropathy; the treatment of which can be very problematic\textsuperscript{67–69} because equilibrium disorders increase the risk of falls, and thus, the risk of bone fractures, which is already high for the low density of the bone mass of these patients.

### Serological and Histological Diagnosis

The diagnosis of CD in elderly patients follows the same guidelines as in young people. Diagnosis is based on the presence of anti-gliadin antibodies (AGAs), endomysial antibodies (EMAs), or tissue transglutaminase antibodies (tTGAs). Moreover, the presence of intraepithelial lymphocytosis, villous atrophy, crypt hyperplasia, and the response to GFD are also used for diagnosis. Titer of tTGAs and improvement of histological lesions are inversely related to age.\textsuperscript{70} This clinical and histological lower expression in adults and elder patients make the diagnosis more complex as compared with children.

The European Society of Pediatric Gastroenterology and Nutrition have formulated guidelines for the diagnosis of CD in children based on high tTG titers without the need for duodenal biopsy.\textsuperscript{71} This is based on evidence of elevated antibody titers that have a high predictive value for villous atrophy, thus avoiding the need for a biopsy. However, the presence of high antibody titers (>10 times normal levels) appears in less than half of the adult cases.\textsuperscript{72} Serological test, such as tTG IgA, has a high sensitivity (~90%) and specificity (~95%) as compared to that of EMA. The TTG IgA evaluation is

| PRESENTATION/COMPLICATION       | FREQUENCY | REFERENCE |
|---------------------------------|-----------|-----------|
| Anemia                          | 60–80%    | 47        |
| Osteopenia/bone disease         | 70%       | 83        |
| Malabsorption                   | 50–80%    | 41        |
| Dermatitis herpetiformis        | 25%       | 52        |
| Celiac hepatitis                | 20%       | 1         |
| Collagenous sprue               | 20%       | 57        |
| Autoimmune thyroiditis          | 15%       | 63        |
| Ataxia and neuropathy           | 15%       | 67        |
| Refractory CD                   | 5%        | 96        |
| Idiopathic dilated cardiomyopathy | 5.7%     | 122       |
| T cell lymphoma                 | 4%        | 98        |
| Type 1 diabetes                 | 3%        | 47        |
recommended as serological screening test for adult CD patients, since AGAs have a low sensitivity and specificity.73 The use of deamidated gliadin peptides (DGPs) as antigens has proven to be much more accurate than the standard AGA test.73–75 In spite of a good sensitivity and specificity of the above reported tests, a certain number of patients with CD cannot be diagnosed on the basis of serology. EMA test, tTG, and DGPs have more false-negative results in patients with mild histological lesions.74,76 Another case of negative test in celiac patient is the deficit of IgA; in this context, IgG isotype of antibodies that are significantly more sensitive compared to tTG IgG can be used.74–76

When there is a clinical suspicion of CD, despite negative serology, patients must be submitted to GI endoscopy to obtain biopsy.74,77 Duodenal biopsy specimens are commonly used to show the presence of enteropathy. The rise of infiltrating intraepithelial lymphocyte, crypt hyperplasia, and grade of villous atrophy (partial or total) are the main histological features of CD.78 Recent studies have shown that in more than 50% of adults, villous atrophy does not improve on GFD unless biopsy is performed after two years of an adequate diet.79 In children, even if information are limited, the recovery of the mucosa occurs in the vast majority (95%) in the first two years after diagnosis.75 There are age-dependent changes in the bowel of elder patients, and therefore, histological diagnosis of CD can differ from that of younger patients.13,41,80 One might delay the intestinal biopsy to an elder patient with comorbidity to confirm the CD suspicion, but often the elder individual is more likely to have an endoscopy to investigate GI symptoms; then, it is often more common to have a histological diagnosis rather than serological. HLA testing would be essential in these seronegative patients.76,78

From a clinical point of view, diagnosing CD in the elderly is quite difficult, not only for family doctors but also for gastroenterologists. In fact, very often, patients present mild clinical symptoms, and if this is associated with a low level of suspicion of CD in older people, clinical examination will be carried out to confirm or rule out more serious conditions (such as malignancy).78 Moreover, the fragility of older patient means that sometimes they are subject to mood disorders and their bowel habits may depend on these changes, especially in patients suffering from irritable bowel syndrome, or, in addition, may be due to aging process. Because of these reasons, older patients with CD often have an average diagnostic delay of about 15–17 years.13,81 In addition, a sign such as anemia in the elderly is highly suspicious of colon cancer rather than CD. Other diseases (bacterial overgrowth syndrome, intestinal ischemia, and exocrine pancreatic insufficiency) may present with malabsorption syndrome, and mimic CD may or occur in celiac patients because of their advanced age, as well. Thus, a complete and accurate differential diagnosis is the basis of the diagnostic process, leading to CD in the elderly.45,82

**Complications**

**Bone disease and fractures.** Bone diseases are mainly due to intestinal malabsorption. The reduction in bone mass is the most common metabolic bone disorder in CD. Up to 70% of adults and elderly patients with CD have a bone mineral density that is less than one standard deviation below normal controls (osteopenia).83 Postmenopausal women are affected more often than those in premenopause.84

The mechanism for osteopenia may be related, in part, to the malabsorption of calcium, causing an increase in the secretion of parathyroid hormone. The increased bone turnover leads to the loss of cortical bone. A decreased absorption of vitamin D could be also experienced by CD patient. Pro-inflammatory and anti-inflammatory cytokines are believed to play an active role in the pathogenesis of osteopenia in CD.

Osteotropic cytokines are involved in bone remodeling because they regulate the differentiation and activation of osteoblasts and osteoclasts; TNF-α and IPN-γ are two cytokine issues during chronic inflammation, and they are associated with increased bone loss. In patients with untreated CD, higher levels of serum cytokines that directly trigger osteoclasts (IL-1, IL-6, and TNF-α) have been detected, while low levels of cytokines that play an inhibitory role (IL-18 and IL-12) are observed.85,86 The receptor activator of nuclear factor kappa-B ligand (RANKL) is basic for bone homeostasis by a dynamic balance between bone-reabsorbing activity performed and the effects of its natural decoy receptor osteoprotegerin (OPG). OPG/RANKL ratio is significantly lower in individuals with CD with recovery of intestinal mucosa than in healthy controls and is positively correlated with low bone mineral density.87 Potential autoantibodies could block the inhibitory effect of OPG on RANKL; however, in another study,88 antibodies against OPG were not found in the serum of patients with CD.

Although celiac patients can improve bone mineral density on GFD, the increase in bone mass in the elderly is limited and may be incomplete. A higher prevalence of fractures also occurs in the peripheral skeleton of elderly celiac.89 Most fractures happen before the diagnosis of CD and commonly occur in those with poor compliance to GFD. Diet is the most important factor that offers protection from the risk of fracture. In a recent population-based study on the long-term fracture risk,90 CD has been linked to an increased risk of fractures before and after diagnosis. Axial and appendicular fractures are a good rationale for early diagnosis of CD and active management of bone disease before the fractures occur.

**Refractory celiac disease.** Refractory celiac disease (RCD) is characterized by severe malabsorption in a patient with histological lesions showing lack of response to GFD, despite firm adherence to the diet. The main reason for lack of response to diet is gluten contamination.82 In the elderly, other diseases, such as exocrine pancreatic insufficiency, bacterial overgrowth syndrome, and lactose intolerance, are involved in the differential diagnosis of RCD,91,92 as well as
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enteritis, collagen sprue, and intestinal mucosa damage from anti-inflammatory drugs.93,94

Patients complain severe malabsorption, progressive weight loss, and significant deficiencies of nutrients and electrolytes. Depending on the phenotype of intraepithelial lymphocytes, the RCD can be classified into two types: polyclonal, or RCD I, and monoclonal with aberrant phenotype of lymphocytes, or RCD II.95 Celiac patients develop an RCD in about 4%–5% of cases, the majority of them being older people. In a study conducted in Mayo Clinic,96 which included 57 patients with RCD with a variable age ranging from 30 to 76 years, it was found that the average age for diagnosis of RCD I and RCD II was 58 and 70 years, respectively. At five years, overall survival was 80% and 45% for patients with RCD I and RCD II, respectively; the main causes of death were refractory state (in RCD I) and enteropathy-associated T-cell lymphoma (in RCD II).97,98 In patients with lymphoma, the prognosis was poor. They also found that old age (greater than 65 years) was one of the prognostic factors with negative effect on the survival in the new staging system proposed for the RCD.96

It should be pointed out that persistent mucosal alterations are common in adult celiac on a GFD and that follow-up biopsies should be done only after two years of diet to document the histological recovery,79 suggesting that the label of refractory can be applied only after a long period (Figs. 1 and 2). Mucosal alterations in RCD are classic endoscopic signs of villous atrophy such as loss of Kerckring’s folds in the duodenum, scalloping of circular folds, and fissuring with a mosaic pattern. These findings are not specific for RCD. The diagnosis of RCD requires a combination of clinical and pathologic findings. Indeed, the diagnosis is made on the basis of strong evidence of CD, supplemented with systematic exclusion of both other causes of nonresponsive CD or villous atrophy and malignancy. Although RCD is a diagnosis of exclusion, it is supported by objective findings in laboratory and histological studies. Duodenal histology shows partial villous atrophy and an increased number of intraepithelial lymphocytes with normal immunophenotype characterized by expression of CD3 and CD8 (type 1 RCD) or duodenal biopsy specimen from a patient with type 2 RCD with villous

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**Figure 1.** Endoscopic duodenal view of a 73-year-old patient with RCD.

**Figure 2.** RCD in the 73-year-old patient: small intestinal mucosal biopsy with frank villous atrophy, showing mild chronic inflammatory infiltrate and some eosinophils in the lamina propria (A/B; hematoxylin/eosin 20× and 40×); CD3 immunostaining highlights an increased number of intraepithelial CD3+ lymphocytes (C/D 20× and 40×).
atrophic and abnormal intraepithelial lymphocytes characterized by expression of CD3, but mostly CD8+.

Malignancy. Occurrence of malignancy is higher in older celiac patients, particularly in those with age ranging from 60 to 80 years. In fact, T-cell lymphomas have been reported to have the strongest association with CD (Fig. 3). Further, the relative risk for lymphoma in CD has been showed to be varying in several studies. Lymphomas and adenocarcinomas are more frequent in patients with CD, even those presenting with silent disease showed a higher mortality rate. GFD seems to have a protective effect on the risk of malignancy in celiac patients. In a series of 119 patients with primary small-bowel non-Hodgkin’s lymphoma (NHL), at least 13 (10.9%) were associated with CD. Treatment with a GFD may ameliorate the prognosis of these cases, eg, by improving the nutritional status and the absorption of drugs given orally.

Celiac Disease and Cardiovascular Risk

Although cardiovascular manifestations play a secondary role in CD in comparison with autoimmune diseases, it seems that being celiac confers an increased risk of death due to cardiovascular events. In fact, it has been shown that individuals with CD are considered at increased risk of death, and other studies have shown an increased risk of incident ischemic heart disease, death resulting from ischemia, or cardiovascular disease. Furthermore, one of these studies reported a twofold increased risk of coronary artery disease in patients with CD, whereas risk of angina and heart failure were raised to 30%–40%. However, it has been estimated that the incidence of cardiovascular disease in patients affected by CD is overall about 5.7%. In an important study of CD screening, carried out on 52 subjects affected by idiopathic dilated cardiomyopathy, 3 out of 52 patients (6%) showed an intestinal villous atrophy. An Italian study including 187 patients, 110 with heart failure and 77 with arrhythmias, for whom a diagnosis of autoimmune myocarditis had been performed, 4.4% were positive to EMAs and tTGAs, as compared to 0.6% of healthy controls. Another study is particularly interesting in this regard, since it identifies QT interval prolongation in one-third of the celiac patients studied, in comparison with no alteration in patients suffering from chronic pancreatitis and other intestinal disorders. In patients with CD, an inverse relationship between QT interval prolongation and blood potassium has been found, hence the recommendation to supplement the diet therapy with potassium administration. The average daily KCl and spironolactone dose was 3.5 ± 1.2 mg/kg.

The biological mechanisms linking CD, chronic heart failure, and other cardiovascular conditions are not fully understood, but several possible pathways have been suggested. One of these could be linked to the evidence that CD patients have a low-grade chronic inflammation, which could drive atherosclerosis and vascular damage. Furthermore, patients following a GFD do not always eat a healthy balance of fats, carbohydrates, and fibers, contributing to the pathogenesis of atherosclerotic process. Regarding this, a case-control study showed that CD is associated with an increased intima-media thickness of the carotid arteries, a well-known intermediate marker of endothelial dysfunction and macrovascular disease.

A further hypothesis linking CD and cardiac damage is the autoimmune mechanism triggered by gliadin, as already showed for other autoimmune disorders associated with CD. Furthermore, the favorable effect of a GFD shows that the improvement in cardiac function may be due to an enhanced absorption of nutrients and oligoelements, playing a beneficial role on myocardial contractility and electrical stability, as well as cardiovascular drug absorption. However, there is also evidence that tTG antibodies have an anti-angiogenic effect that may alter the normal functioning of the vascular system. However, CD, when untreated or when the adherence to a GFD is poor, could lead to malabsorption of nutrients and thus low circulating concentrations of folate or high serum concentrations of homocysteine, which are implicated in the pathophysiology of cardiovascular disease. In fact, villous atrophy can hinder the absorption of several nutrients, such as thiamin, riboflavin, magnesium, calcium, selenium, and car nitine, which are active in myocardial metabolism. In particular, an increment in carnitine levels can be effective for cardiac performance, as some authors have already observed in patients with CD and dilated cardiomyopathy treated with a GFD.
However, regarding the incidence of risk factor for cardiovascular disease among celiac patients, it has been previously observed that mortality due to ischemic heart disease and stroke was lower than that in the general population, thereby hypothesizing a protective action of CD against the above-mentioned conditions, maybe because of the low levels of cholesterol, triglyceride, and fibrinogen. Recently, a nationwide population cohort study carried out on 3790 celiac patients effectively confirmed a reduction in the risk of hypertension and hypercholesterolemia, and thus of myocardial infarction, but showed a slight increase in the risk of stroke.

Therefore, available evidence suggests that cardiovascular manifestations can also be reported in CD. Thus, patients suffering from cardiovascular disease, and especially idiopathic dilated cardiomyopathy, could be reasonable to suspect CD, given the evident favorable effect caused by a GFD on myocardial performance.

### Final Remarks

Despite a paucity of symptoms, such as diarrhea and weight loss, CD has been increasingly recognized in the elderly. Other presentations in the elderly age group include iron deficiency anemia (often refractory to oral iron), autoimmune disorders, bone disease due to osteopenia, including fractures, malignant intestinal disease, especially lymphoma, and finally idiopathic dilated cardiomyopathy. Diagnosis may be delayed due to limited symptoms, a low index of clinical suspicion, or diagnostic difficulties related to important cognitive impairment that often affects elderly people. Although for these patients, the GFD is the key of clinical management, elderly patients sometimes are scarcely adherent to diet.

Patients should be referred to specialists to ensure the better management of the disease and related complications. Micronutrients, such as iron, calcium, vitamin D supplementation, and vitamins, should be part of a modified GFD for the elderly patients. All other therapeutic interventions that limit malabsorption and avoid complications should be considered part of a management strategy.

### Author Contributions

Conceived and designed the experiments: MC, AL. Analyzed the data: MC, GCM. Wrote the first draft of the manuscript: GCM, AL. Contributed to the writing of the manuscript: MC, GCM, AL. Agree with manuscript results and conclusions: MC, AL. Jointly developed the structure and arguments for the paper: MC, AL. Made critical revisions and approved final version: MC, GCM, AL. All authors reviewed and approved of the final manuscript.

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