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Atherosclerosis and cardiovascular involvement in celiac disease: the role of autoimmunity and inflammation

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Abstract. – OBJECTIVE: The aim of this review is to explore the evidence about the association among celiac disease (CD), atherosclerosis (AS) and cardiovascular (CV) diseases, and the role of inflammation in this connection.

MATERIALS AND METHODS: A systematic literature search was conducted using PubMed, EMBASE, and Cochrane Library for the association among CD, AS and CV diseases.

RESULTS: Several studies reported the association of CD with accelerated AS, as evidenced by the alterations of a number of parameters indicative of subclinical AS, as increased carotid artery intima-media thickness, endothelial dysfunction and increased arterial stiffness. In addition, recent evidence reported an increase of CV diseases prevalence in CD patients respect to controls, many of which including ischemic diseases as acute myocardial infarction and angina pectoris, as well as death from ischemic heart disease, and, more rarely, stroke for cerebrovascular involvement. Other not-ischemic CV diseases associated with CD are represented by dilated cardiomyopathy, atrial fibrillation, and myocarditis.

CONCLUSIONS: On the basis of the reported association among CD, AS and CV diseases, we suggest to perform a more detailed CV risk assessment in all CD patients than what is currently being achieved in clinical practice, in order to scan and treat modifiable CV risk factors in these patients. In particular, we suggest to resort to instrumental techniques to detect AS in the subclinical stage, in order to prevent AS development and CV diseases in CD patients.

Key Words:
Inflammation, Celiac disease, Atherosclerosis, Carotid artery intima-media thickness, Endothelial dysfunction, Arterial stiffness.

Introduction

Celiac Disease

Celiac disease (CD) is an autoimmune enteropathy occurring in genetically susceptible individuals, induced by the ingestion of gluten-containing foods and characterized by intestinal malabsorption and total or subtotal atrophy of intestinal villi[1].

CD is considered a model of multifactorial disease, resulting from the interaction between gluten and immune, genetic and environmental factors[2], with an abnormal immune response directed against tissue transglutaminase (tTG) as auto-antigen[3,4]. The most common serological markers to screen CD are represented by the anti-tTG and anti-endomysium auto-antibodies[5,6]. HLA-DQ2 and HLA-DQ8 molecules represent the most important, so far known, predisposing genetic factors, along more than 60 additional susceptible genes described by genome-wide association studies[7]. Recent have reported an increase in CD prevalence, up to 2% in Western countries[5]. Previously, CD was considered a rare malabsorption syndrome of childhood, but now is recognized as a common condition that may be diagnosed at any age and that affects many organ systems[8-10]; nowadays, about 20% of newly diagnosed cases occur in patients who are older than 60 years of age. In addition, the typical gastrointestinal clinical disorders, represented by diarrhea and weight loss, are disappearing, while the extra-intestinal ones, including iron-deficiency anemia, osteoporosis, dermatitis herpetiforme and neurologic disorders, are increasing[11-13]. The gut inflammation, as a result of the immunologi-

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cal response to gluten, and the consequent abnormal intestinal permeability, increase antigenic exposure and then autoantibody production: this may represent the basis of the connection of CD with other autoimmune diseases[14-18]. Furthermore, among subjects with undiagnosed or poorly treated CD, a high rate of mortality was observed, firstly linked to increased risk of malignancy, probably due to reduced absorption of important nutrients[18]. Finally, the systemic pattern of inflammation and the diffuse immune activation described in CD could be considered as pivotal mechanisms, which could explain the association of CD with atherosclerosis (AS) and cardiovascular (CV) diseases[19,20]. In fact, the presence in peripheral blood of untreated CD patients of T lymphocytes specific to tTG-deamidated gluten peptides suggests that the inflammatory responses of the mucosal immune system in CD patients are not limited to the small intestine[21,22]. Furthermore, these patients presented a memory cell phenotype and expressed β7 integrin as a marker of gut homing[23,24]. Moreover, growing evidence has led to the hypothesis that metabolites derived from gut microbiota, widely influenced by presence of dietary gluten, can play a potential key role in the modulation of autoimmune and inflammatory diseases by activating the Toll-like receptors in the intestine with consequent increased secretion of pro-inflammatory cytokines, finally resulting in increased risk of developing AS[25-27].

Atherosclerosis

Atherosclerosis (AS) is a chronic and progressive disease, which etiopathogenesis has dramatically changed in the last decades on the basis of the new findings on molecular and cellular biology. Several pathophysiologic observations in humans and animals have led to the formulation of the response-to-injury hypothesis of AS, which proposes that endothelial dysfunction is the first step in AS. Possible causes of endothelial dysfunction leading to AS include dyslipidemia, free radicals caused by cigarette smoking, hypertension and diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations and combinations of these factors. The endothelial dysfunction leads to compensatory responses that alter the normal homeostatic properties of the endothelium[28]. The subsequent inflammation of the arterial wall, involved in the formation, progression and the possible occurrence of complications of the atherosclerotic plaques, is promoted by both innate and adaptive Th1-driven immunity and coordinated by several pro-inflammatory cytokines. The inception of the AS process is the sub-endothelial accumulation of oxidized low-density lipoprotein, which stimulates the endothelial cells to produce pro-inflammatory molecules, including adhesion molecules and growth factors, largely involved in the progression of the AS processes. Endothelial cells and smooth muscle cells contribute to leukocyte recruitment, vascular remodeling and to the perpetuation of inflammation stimulating the release of pro-inflammatory cytokines and chemokines[29].

From a clinical perspective, the atherosclerotic process presents a long asymptomatic phase. However, during this subclinical stage, AS presence can be identified by several non-invasive methods, including B-mode ultrasonography with carotid artery intima-media thickness (cIMT) measurement, endothelial dysfunction and arterial stiffness.

The presence of increased cIMT represents a marker of early arterial injury that is not responsible of any hemodynamic alterations or clinical manifestations; however, it is associated with coronary risk factors[30] and increased risk of CV events[31,32]. Moreover cIMT is a useful atherosclerotic surrogate end-point for therapeutic interventions[33]. Endothelial dysfunction is due to reduced nitric oxide production by endothelial cells, and is considered an early event of AS that precedes structural atherosclerotic changes in the vascular wall[28,29]. It can be assessed by the measurements of flow-mediated vasodilatation (FMD). Impaired FMD is predictive of CV events: several studies showed a positive correlation of FMD with traditional CV risk factors, such as hypertension, dyslipidemia, diabetes mellitus, smoking habit, sedentary behavior and inflammation[34,35]. Furthermore, it has been demonstrated that impaired FMD predicts CV morbidity and mortality independently of traditional CV risk factors and the Framingham risk score[36]. Arterial stiffness, assessed by noninvasive pulse wave velocity (PWV) evaluation, is another independent predictor of CV diseases. Increased arterial stiffness is correlated with the aging process and with AS risk factors, such as hypertension, diabetes, dyslipidemia, obesity and smoking.

Several lines of evidence suggest that a condition of accelerated AS can be observed precociously in several conditions, in particular in autoimmune diseases, and that the early AS observed in these conditions, cannot be ex-

plained exclusively by traditional CV risk factors[37]. In fact, autoimmune diseases and AS share a number of common pathogenic pathways. Chronic inflammation underlies both diseases with increased numbers of macrophages, dendritic cells, and B and T lymphocytes. A chronic inflammatory background mediated by the Toll-like receptors and inflammatory/IL-1 pathways, as seen in auto-inflammatory diseases and endothelial dysfunction, are early steps that may lead to the development of atherosclerotic plaques. The aim of this review is to explore the published evidence on the link among CD, AS and CV diseases, and the role of inflammation in this connection.

Materials and Methods

A systematic literature search was conducted by using PubMed, EMBASE, and Cochrane Library for the association among CD, AS and CV diseases: a total of 23 studies were included for review: 17 specifically conducted evaluating CV risk factors and CV diseases in CD patients, and 6 providing relationship between CD and markers of AS (Table I).

Results

Atherosclerosis in Celiac Disease

Several studies have investigated the presence of subclinical AS in CD patients. De Marchi et al [38], in their pilot study, analyzed data from 20 patients at first diagnosis of CD and found that CD patients seem to be exposed at potentially increased risk of early AS compared with healthy, as evidenced by a significant increase in cIMT and a significant decrease in FMD in the firsts. They also demonstrated that both parameters improved by 6-8 months of gluten free diet. Moreover, compared with baseline, a significant increase in both total plasma cholesterol and high-density lipoprotein cholesterol concentrations (without modification on low-density lipoprotein cholesterol concentrations) were observed after gluten abstinence, as well as a reduction of C reactive protein blood levels[38].

Sari et al[39] studied the endothelial function through FMD in 36 patients with CD and found an impaired FMD in CD patients compared with healthy controls. They also investigated signs of systolic dysfunction by measure of ejection fraction and heart chambers dimensions through two-dimensional and M-mode echocardiography, finding no significant difference between CD patients and controls.

Signs of subclinical atherosclerosis, assessed by cIMT in patients with CD, alone or associated with type I diabetes mellitus (T1DM), were evaluated by Pitocco et al[40], which found increased cIMT in CD patients, compared with age and sex-matched healthy controls. Patients with both T1DM and CD develop more severe subclinical forms of AS compared with those presenting only with T1DM or CD, suggesting that the association of these autoimmune diseases might accelerate the atherosclerotic process. Furthermore, patients with CD or T1DM only, presented a similar cIMT. In addition, higher C reactive protein blood levels, a well known marker of low grade inflammation, were observed in patients with both T1DM and CD, or T1DM and CD alone, compared with healthy subjects.

Korkmaz et al[19] studied arterial stiffness using PWV in 58 adult CD patients without other CV risk factors compared with a control group, finding an increase of arterial stiffness and homocysteine, erythrocyte sedimentation rate, C-reactive protein, insulin and insulin resistance in patients with CD.

Finally, Demir et al[41] found normal PWV and cIMT as parameters of subclinical AS in a treated pediatric CD population suggesting that gluten free diet seems to have a beneficial effect on premature AS.

Cardiovascular Diseases in Celiac Disease

Among CD associated diseases, CV involvement represents a topic of growing interest in the last years. In particular, some studies[42,43] have shown an increased risk of incident ischemic heart disease (IHD) and death resulting from IHD in CD patients. This association seems to be primarily linked to the presence of a systemic pattern of inflammation and a diffuse immune activation as pivotal mechanisms[19,44]. A concomitant presence of traditional CV risk factors, such as dyslipidemia and hypertension, could justify increased risk of CV diseases in these subjects[45]. Moreover, the presence of other known CV risk factors as vitamin B12, folic acid deficiency that entails high homocysteine levels, and psychological stress, could justify increased risk of ischemic disease[46]. In addition, the typical malabsorption of CD subjects may also increase the CV risk by reducing the

Table I. Features of the main studies included in the review.

Title and Author	Journal and publishing year	Type	Main findings
Prevalence of coeliac disease in idiopathic dilated cardiomyopathy. Curione et al[54]	Lancet 1999	Cohort study	Increase of CD prevalence in patients with idiopathic cardiomyopathy.
Cardiomyopathy in Danish patients with coeliac disease. Fonager et al[55]	Lancet 1999	Population-based cohort study	Increasing evidence for an association between CD and cardiomyopathy.
Celiac disease associated with autoimmune myocarditis. Frustaci et al[59]	Circulation 2002	Cohort study	Significant prevalence of common autoimmune process toward antigenic components of the myocardium and small bowel in patients with myocarditis.
Risk of vascular disease in adults with diagnosed celiac disease: a population-based study. West J et al[47]	Aliment Pharmacol Ther 2004	Population-based cohort study	Lower prevalence of hypertension and hypercholesterolaemia in CD adults compared with the general population.
Celiac disease prevalence in Brazilian dilated cardiomyopathy patients. De Bem et al[56]	Dig Dis Sci 2006	Cohort study	CD screening recommended in patients with cardiomiopathy using IgA-EMA test.
Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. Viljamaa et al[42]	Dig Liver Dis 2006	Population-based cohort study	Non-Hodgkin lymphoma emerged in patients with undiagnosed or poorly treated CD.
Vascular disease in a population-based cohort of individuals hospitalised with celiac disease. Ludvigsson et al[48]	Heart 2007	Population-based cohort study	Positive association between CD and later CV disease.
Association between coeliac disease and cardiovascular disease. Wei et al[52]	Aliment Pharmacol Ther 2008	Community-based cohort study	CD associated with an increased risk of CV outcome.
Combined atherogenic effects of celiac disease and type 1 diabetes mellitus. Pitocco et al[40]	Atherosclerosis 2011	Case-control study	Greater c-IMT in CD patients compared with healthy individuals. Non-invasive monitoring of c-IMT in CD might be useful in preventing CV disease.
Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. Ludvigsson et al[50]	Circulation 2011	Population-based cohort study	Individuals with CD or small intestinal inflammation are at increased risk of incident ischemic heart disease.
Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. Emilsson et al[58]	Eur Heart J 2011	Population-based cohort study	Increased risk of atrial fibrillation in patients with CD, verified by intestinal biopsy.
The Evaluation of Endothelial Functions in Patients with Celiac Disease. Sari et al[39]	Echocardiography 2012	Case-control	Endothelial dysfunction in CD patients.
Risk of stroke in 28,000 patients with celiac disease: a nationwide cohort study in Sweden. Ludvigsson et al[53]	J Stroke Cerebrovasc Dis 2012	Population-based cohort study	Small increased risk of stroke in CD patients.
Risk of idiopathic dilated cardiomyopathy in 29000 patients with celiac disease. Emilsson et al[57]	J Am Heart Assoc 2012	Population-based cohort study	Moderately but not statistically significantly increased risk of idiopathic dilated cardiomyopathy in patients with biopsy-verified CD
Impact of gluten-free diet on cardiovascular risk factors. A retrospective analysis in a large cohort of coeliac patients. Zanini et al[49]	Dig Liver Dis 2013	Cohort study	A gluten-free diet may affect CV risk profile in CD patients.

Table Continued

Table I *(Continued)*. Features of the main studies included in the review.

Title and Author	Journal and publishing year	Type	Main findings
Young adults with coeliac disease may be at increased risk of early atherosclerosis. De Marchi et al[38]	Aliment Pharmacol Ther 2013	Case-control study	Increased risk of early atherosclerosis in CD, with normalization of gut mucosal alterations after gluten abstinence.
Cardiovascular disease risk factor profiles in children with celiac disease on gluten-free diets. Norsa et al[45]	World J Gastroenterol 2013	Cross-sectional multicenter study	Importance of CV diseases screening and the need for dietary counseling targeting CV diseases prevention in CD children.
Increased arterial stiffness and its relationship with inflammation, insulin, and insulin resistance in celiac disease. Korkmaza et al[19]	Eur J Gastroenterol Hepatol 2015	Case-control study	Increased arterial stiffness, inflammation and metabolic parameters in CD patients.
Carotid intima-media thickness and arterial stiffness as early markers of atherosclerosis in pediatric celiac disease. Demir et al[41]	Turk J Pediatr 2016	Cross-sectional single center study	Decreased cIMT in CD patients undergoing strict gluten-free diet.

CD = celiac disease; CV = cardiovascular; cIMT = carotid artery intima-media thickness.

bioavailability of CV protective drugs and essential nutrients, modifying cardiac conduction and contractility. Furthermore, it is surprising that some studies have reported that CD subjects adhering to a gluten-free diet, despite of presence of factors that may protect against ischemic diseases (lower cholesterol levels, lower blood pressure levels, and potentially fewer smokers), have rates of myocardial infarction and stroke not substantially different respect to the general population[47-49].

In a Swedish population-based cohort study, Ludvigsson et al[50] found a 19% increased risk of IHD in individuals with CD. This study also found a 28% increased risk of IHD in individuals with small intestinal inflammation but no villous atrophy, and a 14% increased risk of IHD in individuals with normal mucosa but positive CD serology; however, in latent CD, there was no association with myocardial infarction or with death from IHD, but only with incident angina pectoris. Also, cerebrovascular involvement has been reported in adults and children with CD. In particular, a pediatric case has been described in a child who had a recurrent transient hemiplegia; antiendomysial immunoglobulin A antibodies reacting with cerebral vasculature have suggested an autoimmune mechanism for this CD associated to vasculopathy[51]. On the other hand, other studies have arisen different conclusions, founding reduced risk for stroke than that observed in other large population-based studies[47,52]. This was restricted mainly to the first year after diagnosis, suggesting that CD does not seem to be a major risk factor for stroke, neither in children nor in adults[53].

Other not-ischemic CV diseases have been reported in association with CD. Some studies have reported an increased prevalence of CD in patients with dilated cardiomyopathy (DCM). However, the number of these patients has been relatively small, ranging from 1 to 4 patients with both CD and DCM diagnoses in each study[54-56]. A nationwide study by Emilsson et al[57] identified 17 patients with CD and patient chart – validated idiopathic DCM, finding a moderately but not statistically significantly increased risk of idiopathic DCM in patients with biopsy-verified CD. The positive association between CD and DCM may have several explanations, including nutritional deficiencies, but, at first, the most plausible explanation is that both conditions might be mediated through inflammation and autoimmune mechanisms.

In another nationwide study, Emilsson et al[58] found a positive association between CD and atrial fibrillation founding that CD patients were at 30% increased risk of having atrial fibrillation diagnosis when compared with the general population. This association was strongest around the

time of diagnosis suggesting that inflammation and immune-mediated disorders might increase the risk of atrial fibrillation.

Finally, Frustaci et al[59] showed the presence of an intestinal inflammatory disease in 4.4% of a large population of patients with myocarditis, with a prevalence that was 14 times higher than control subjects. A combination of villous atrophy with lymphocytic infiltration of the small bowel mucosa was documented in 9 patients, and in these patients, clinical manifestation of myocarditis represented by heart failure markedly improved after a combination of gluten-free diet and immunosuppressive therapy.

Conclusions

CD can be associated with an increased risk of AS. The etiopathogenic foundation of this association mainly dates back to the presence of a systemic pattern of subclinical inflammation. However, other elements such as the decrease of certain nutrients like vitamin B and folic acid, which result in increased serum levels of homocysteine, a known CV risk factor, may be involved. The malabsorption, typical in CD, may also increase the CV risk in patients who already suffering from CV diseases, because of the poor bioavailability of protective drugs for the CV system. Gut microbiota could be involved in the association between CD and its increased risk of AS. The modulation of gut microbiota by a gluten free diet might impact the atherosclerotic processes in these patients. On the other hand, in patients suffering from CD, adherence to a strict gluten free diet can lead to an improvement also in terms of CV safety. In recent years, various studies have confirmed the presence of accelerated AS and CV diseases in patients with CD.

Currently, the clinical guidelines addressing the diagnosis, treatment, and overall management of patients with CD, do not suggest routine CV risk assessment in these patients[60].

Consequently, recommendations on the management of CD patients should include a more detailed CV risk evaluation, in order to scan and treat CV modifiable risk factors in these patients than what is in current practice. Moreover, we suggest to resort to instrumental techniques to detect AS in the subclinical stage, such as non-invasive methods, including cIMT, endothelial dysfunction and arterial stiffness measurement, in order to prevent AS development and atherosclerotic CV disease in these patients. Furthermore, once again we would like to underline the importance of gluten free diet, which seems to revert to normal the observed alterations, even in terms of CV risk reduction.

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Conflict of Interest Statement

All the authors do not have potential conflicts of interest related to the subject matter of the manuscript.

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