REVIEW ARTICLE

Gluten-free diet in celiac disease: protective or providing additive risk factors for the development of cardiovascular disease?

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ABSTRACT

Celiac disease is a common disease affecting mainly the small intestine, but also involving other organs, with a broad range of manifestations of variable severity. The only available treatment is lifelong adherence to a gluten-free diet.

Cardiovascular diseases have multifactorial etiologies and are the leading cause of death in developed countries. This article reviews the available evidence on the relationship between celiac disease, a gluten-free diet, and cardiovascular disease and its risk factors.

KEY WORDS: *Celiac disease, Gluten-free diet, Cardiovascular disease, Cardiovascular disease risk factors*

Received: November 13, 2011; Accepted: February 21, 2012

INTRODUCTION

Celiac disease (CD) is a common disease affecting mainly the small intestine, but involving other organs as well, with a broad range of manifestations of variable severity. Both genetic and environmental factors are implicated in the development of CD. The disease is triggered and sustained in genetically susceptible individuals by an immunological response following the ingestion of wheat gluten and similar alcohol-soluble proteins (prolamins) (1). The worldwide prevalence of CD is difficult to estimate and ranges from 0.5% to 3% of the general population in Europe and the United States (2-4).

CD may present at any stage of life and can be divided into 2 types: classical CD, which is particularly common among children and is characterized by malabsorption (diarrhea, failure to thrive, steatorrhea, lack of appetite, vomiting and deficiencies in fat-soluble vitamins, iron, calcium and folic acid) and atypical CD, more common during adolescence and adulthood, which may present with laboratory abnormalities (mainly iron-deficiency anemia), irritable bowel, osteopenia, and/or fertility problems, or may be identified incidentally during screening of high-risk individuals.

CD is currently diagnosed using IgA anti-tissue transglutaminase (tTG) antibodies followed by confirmatory biopsies of the small intestine with compatible histopathological findings (5, 6). While official guidelines have not yet addressed the issue, in the case of IgA deficiency, often the diagnosis of CD is raised with the use of IgG tTG or with IgG anti-deaminated gliadin peptide antibodies (7), followed by intestinal biopsy.

Currently, the only effective treatment for CD is strict, lifelong elimination of gluten from the diet, which is usually

followed by rapid clinical improvement, especially in children (8). The gluten-free diet (GFD) is based on the elimination of all products containing wheat, barley, and rye and of any product deriving from these cereals. Because a lifelong GFD is difficult to follow, the reported compliance rates are low, ranging from 40% to 80% (9, 10).

A GFD should ideally be a varied diet with a balanced macronutrient and micronutrient content, pleasant, and sufficient to meet an individual's nutritional needs. However, it is known that some nutrient deficiencies (vitamin B6, vitamin B12, folic acid) are frequent after having followed a GFD for years, mainly due to low fortification of specific foods (11). Furthermore, it has been reported in the literature that limiting the consumption of gluten-containing carbohydrates leads many patients to increase their fat consumption (12). These issues point out the importance of early referral to an experienced nutritionist and periodic follow-up, but also raise the possibility that a GFD may have an effect on the risk of developing cardiovascular disease (CVD).

The World Health Organization has recently reaffirmed that CVD, including ischemic heart disease (IHD), stroke and other cerebrovascular diseases, is the leading cause of death, particularly in developed countries (13). Although there are studies that have shown an increased risk of IHD or other CVDs in patients affected by CD, the evidence of an association between CD and these diseases is still contradictory. We therefore present the available evidence exploring the relationship between CD, GFD, and CVD risk.

Our search strategy included a Medline search using the terms celiac, coeliac, gluten-free diet, and cardiovascular disease, stroke, myocardial infarct, hypertension, hyperlipidemia, hypercholesterolemia. The results were screened for relevance and the relevant articles were reviewed.

CELIAC DISEASE AND GLUTEN-FREE DIET: EFFECT ON CARDIOVASCULAR DISEASE RISK FACTORS

Coronary heart disease and stroke are multifactorial conditions for which many risk factors have been described (14). The modifiable risk factors considered most important are hypertension, hypercholesterolemia, obesity, high-fat diet and physical inactivity, all of which are highly prevalent in the general population of developed countries. Hence the importance of analyzing their relationship with CD and their modification after the introduction of GFD in order to assess the cardiovascular risk in people affected by CD.

Effect on hypertension

Hypertension is reported to be the single-most influential risk factor for stroke (14) and is a leading cause of CVD. The relationship between hypertension and CD has not been thoroughly investigated in the literature. A report by Lim et al (15) of a patient with a 1-year history of hypertension, incidentally found to have untreated CD, was the first to describe this association. The novelty of this case was that the hypertension resolved following the introduction of a GFD. The authors, noting that elevated homocysteine levels in their patient normalized following the dietary modification, postulated that this may have been the underlying mechanism of the hypertension. However, Hallert et al (11), in a small study of CD patients (n=30) with biopsy-proven remission on long-term GFD, found that these patients had higher levels of homocysteine compared with the general population.

West et al (16) reported lower blood pressure and lower cholesterol serum levels in subjects with undetected (and therefore untreated) CD as determined by positive anti-endomysial antibody titers, which at the time the study was performed was the available diagnostic serological test. A survey by Thomason et al (17) demonstrated less frequent utilization of antihypertensive drugs (odds ratio [OR]: 0.40; 95% confidence interval [CI] 0.20-0.77) in CD patients, with no mention, however, if the patients maintained the GFD.

Subsequently, West et al (18) reported that CD patients on GFD have a lower prevalence of hypertension than the general population (11% vs 15%, OR 0.68, 95% CI 0.6-0.76). This difference could only partially be explained by the higher body mass indices (BMIs) of the control patients. The study by West et al, while not without methodological limitations addressed in the publication, demonstrated in a broad population-based cohort, a significant effect of CD on the presence of hypertension. Unfortunately, the study was not structured to identify whether CD or GFD were responsible for the observed differences in the study group. Despite these findings the mechanistic role of CD or GFD on hypertension remains unclear.

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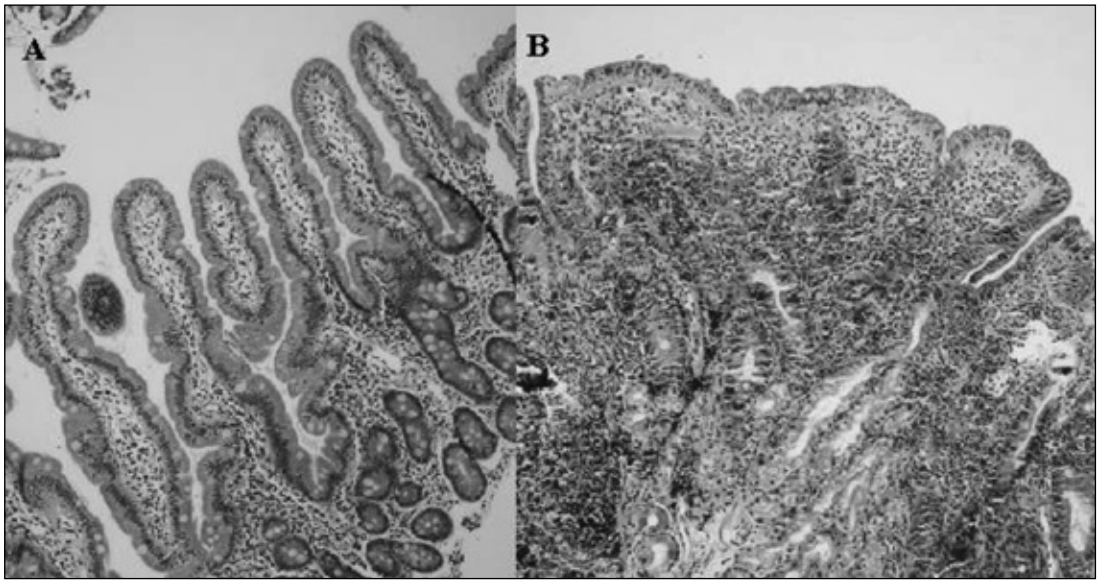

Fig. 1 - *Histological findings in celiac disease. A) Normal mucosa from the duodenum (second part); hematoxylin & eosin. B) Celiac disease, Marsh grade 3C from the duodenum (second part) showing total villous atrophy, crypt hyperplasia, intraepithelial lymphocytes, and submucosal infiltrate.*

Effect on obesity and body composition

Although CD has traditionally been considered a malabsorptive disorder associated with diarrhea and weight loss, these symptoms are nowadays less frequently seen beyond childhood (19, 20). In a brief prospective study from Northern Ireland in 1998, Dickey and Bodkin (21) reported that only a minority of newly diagnosed CD patients aged 16-65 years had low BMIs at presentation, in contrast to 67% of men (n=10) and 20% of women (n=7) who were overweight (BMI >25). This shift could be attributed to increased awareness of physicians diagnosing the disease, to the nonmalabsorptive signs and symptoms of CD, as well as to the availability of more sensitive and specific serological markers with the subsequently more frequent diagnosis of CD in patients with normal or elevated BMIs. In addition, the radical change in nutrition and lifestyle in the developed world could be partially responsible for this observation. Furthermore, the general increase in the prevalence of obesity in the general population (22) must be considered in the context of the drift of body composition of newly diagnosed CD patients. Based on these and other reports, an interesting debate started in the literature about the influence of GFD on obesity and weight status of CD patients. A further study by Dickey et al in 2006 (23), on patients who were overweight at the time of diagnosis, demonstrated that a GFD could lead to further weight gain that may represent a potential cause of morbidity. However, a recent study by Cheng et al (24) underlines the positive effects of GFD on the BMI of CD patients through gain of weight in underweight patients and loss of weight in those who are overweight. The possible discrepancies between the outcomes of the last 2 studies may have stemmed from the fact that the patients from the second study were treated in a dedicated center and therefore may have received instruction from more experienced dieticians or at more regular intervals.

Regarding the pediatric population, data also remain inconclusive. There are several case reports of children and adolescents who were diagnosed with CD and obesity (25-27). The data on the prevalence of obesity in children with CD are still non concordant. Figures vary from 0.45% in the Turkish population (28) to 5% in a recent study from the United States (29). Another recent study published in 2010 (30) addresses the impact of GFD on weight status in children. In concordance with the study by Dickey et al (23), this study of a cohort of children diagnosed with CD showed an increase in the fraction of overweight children following the introduction of GFD (11% vs 21%; p=0.03).

In addition to weight and BMI, analyses of body composition of CD patients have also been reported. All published studies concur that at the time of diagnosis of CD, there is a reduction of lean mass, fat mass and bone mass compared with these parameters in healthy subjects. The introduction and strict adherence to GFD resulted in rapid normalization of all these parameters (31-33).

These important studies on the anthropometry of CD patients and the effect of GFD on anthropometric

measurements do not reach a unanimous conclusion; however, the data point towards a general pattern in which a strict GFD tends to increase weight and normalize body composition parameters in CD patients. This observation must be carefully taken into consideration by clinicians practicing in regions with high rates of obesity, especially in developed countries where additional risk factors for CVD are often present. The effect of GFD on the BMI of these patients still remains unclear. Prospective longitudinal studies of the obese subset of CD patients, whether at the time of diagnosis or on established GFD, will provide important guidance to clinicians.

Effect on lipid profile

Armed with the knowledge that the intestine has an active role in lipoprotein metabolism, not only as an absorptive organ but also as a source of chylomicron production and lipoprotein metabolism (34), investigations into the relationship between CD and lipid profile have been performed. In 1990, Rosenthal et al (35) compared a cohort of Israeli children diagnosed with CD with a control group of children having other intestinal diseases. They found that CD patients had lower plasma levels of triglycerides yet higher cholesterol content in LDL, while total cholesterol, high density lipoprotein cholesterol (HDL-C), and very low density lipoprotein cholesterol (VLDL-C) were similar. Furthermore, significantly lower protein content in VLDL was found. All of these parameters reverted to normal levels following institution of GFD. The authors concluded that the data suggested that, at the time of diagnosis, CD patients have lower levels of cholesterol than the general population not only because of the nonspecific malabsorptive effects of CD, but also because of an alteration in enterocyte function indicated by the variant apolipoprotein synthesis (35). A similar study, from Italy, was published 1 year later (36). This study investigated plasma lipid levels in children with CD at diagnosis and after introduction of GFD and compared them to those of a group of children with irritable bowel syndrome (IBS). The outcomes differed from those of Rosenthal et al (35): the Italian group found that plasma total cholesterol and HDL-C levels were significantly lower and triglycerides higher in untreated pediatric CD patients compared with the IBS controls. Plasma HDL-C significantly increased after some months of GFD. In this article the differences between the Italian and Israeli cohorts were discussed: possible differences in local diet, climate and physical exercise were offered as possible explanations for the differences in lipid levels found in the 2 investigated populations (36). Already in the early 1990s, these 2 articles were unearthing a still ongoing debate concerning the lipid profiles of CD patients and their modification by GFD.

More recent studies have emphasized that lower concentrations of total cholesterol and HDL-C are frequently observed in untreated CD patients. GFD seems to normalize the lipid profile, by increasing the levels of both total cholesterol and HDL-C (37, 38). Brar et al (39) described improvement of the lipoprotein profile in patients on a GFD, with an increase in HDL-C associated with a reduction of the LDL/HDL ratio. Moreover, 2 additional studies pointed out a rapid increase in HDL-C blood levels following a single year of GFD without a concomitant increase in total cholesterol. These studies suggest that any increased risk for CVD in individuals with CD is unlikely due to an adverse lipid profile after treatment with GFD (40, 41).

Although these studies provide good evidence of a protective role of GFD on the lipid profiles of CD patients, the debate in the literature is still open as to the role of dietary lipid intake in CD patients on GFD. A number of recent publications have in fact observed higher consumption of lipids in the diets of treated patients compared with healthy controls (12). This tendency might be accounted for by the need of patients to eat high-fat diets (e.g. eggs, meat, and cheese) in order to achieve satiation while on GFD. Furthermore, gluten-free products which mimic gluten-containing originals (bread, pasta and pizza) are often considered unpalatable by adult patients in particular (42, 43). These data raise questions about the “health benefit” of the GFD. Whether the GFD is “heart healthy” or whether its high fat content may represent a treatment-related risk factor for developing CVD remains to be addressed in future studies.

CELIAC DISEASE AND CARDIOVASCULAR DISEASES

The initial report by Whorwell et al (44) on possibly reduced mortality from IHD in CD patients found a significant decrease in death from IHD in the studied population compared with the expected number of deaths ($p<0.05$). The study did not report whether or not the enrolled CD

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patients were on GFD (44). This was just the first of several subsequent publications which debate the relationship between CD and cardiovascular morbidity and mortality. West et al (18), as previously mentioned, performed a population-based study exploring the relationship between CD and vascular diseases. Reporting on 3590 CD patients and nearly 18,000 age-matched controls in the UK, they found a decreased risk of both hypertension (OR 0.68; 95% CI 0.60-0.76) and hypercholesterolemia (OR 0.58; 95% CI 0.47-0.72) in adults with diagnosed CD and a slightly decreased risk of myocardial infarction (18). The CD cohort of patients was assumed to be on GFD, and the authors suggested that GFD attenuates the relationship of CD with myocardial infarction by enhancing intestinal cholesterol absorption. Surprisingly, a slightly elevated risk of stroke was also found (hazard ratio [HR] 1.29; 95% CI 0.98-1.70). The authors postulated that their findings may be explained either by the high prevalence of CD reported in idiopathic cardiomyopathy, suggesting that the mechanism might be arrhythmogenic or thromboembolic (45), or by the neurotoxic effects of gluten in CD patients (46). The finding of increased prevalence of stroke is in agreement with a recent study by Ludvigsson et al (47) which underlined that the risk of stroke in CD patients was associated with the degree of microscopic inflammation in the gastrointestinal tract. Individuals with CD were at an increased risk of stroke compared to individuals with potential CD (normal mucosa [Marsh 0] and positive celiac serology) (HR 1.35; 95% CI 1.01-1.79), but at lower risk than individuals with inflammation but without villous atrophy (Marsh 1-2; HR 0.88; 95% CI 0.79-0.97). This finding supports the idea that a GFD may reduce the risk of future stroke in CD by mitigating the small intestine inflammation (47).

Interestingly, in a recent publication, Godfrey et al (48) did not find any evidence for increased IHD mortality in undiagnosed CD patients. In that study, no difference in the prevalence of IHD was found between undiagnosed CD cases and seronegative controls (OR 1.03; 95% CI 0.58-1.83) (48). Another recent study could not identify significant differences in mortality from cardiovascular disease in patients with undetected CD (49).

In contrast to these results, other studies conclude that individuals with CD are at increased risk for both IHD and CVD. The pioneers of this hypothesis were Peters et al (50) who, in a follow-up period from 1965 until 1994, studied the causes of death in patients with CD in a population-based Swedish cohort. Based on a cohort of 10,000 CD patients and 81,000 healthy matched controls they reported that the mortality risk for CVD was increased in CD patients (standardized mortality ratio [SMR] 1.6; 95% CI 1.4-1.8). The risks were comparable for all subsets of CVD: IHD (SMR 1.5; 95% CI 1.3-1.8), other nonpulmonary heart disease (SMR 2; 95% CI 1.5-2.7), and cerebrovascular disease (SMR 1.4; 95% CI 1.1-1.9).

More recently, other studies confirmed these findings. Ludvigsson and his team ardently supported the theory of an association between CD and increased morbidity and mortality from CVD, and demonstrated their findings in 4 reports (51-54), all published in the past half decade. In 2007 they found that CD was associated with myocardial infarction (HR 1.27; 95% CI 1.09-1.48), angina pectoris (HR 1.46; 95% CI 1.25-1.70), heart failure (HR 1.4; 95% CI 1.22-1.62), brain hemorrhage (HR 1.40; 95% CI 1.05-1.88) and ischemic stroke (HR 1.35; 95% CI 1.14-1.60) in a population-based cohort of individuals hospitalized with CD (51). However, there was no mention of GFD in that report. In 2009 they reported finding increased mortality from CVD in patients with CD (HR 1.19; 95% CI 1.11-1.28) and with inflammation but without villous atrophy (Marsh 1-2) (HR 1.35; 95% CI 1.25-1.45) (52). These findings were reinforced by 2 nationwide cohort studies from 2011. The first report showed an increased incidence of death from IHD in patients with CD (HR 1.22; 95% CI 1.06-1.40) (53). The second showed that CD patients were at 30% increased risk of having atrial fibrillation diagnosed when compared with the general population (54), a finding which had previously been reported (15). The postulated mechanism of action presented in these studies was the role of inflammation, universally present in untreated or inadequately treated CD, in the pathophysiology of CVD.

Another study published by a group of British physicians (55) found an association between CD and cardiovascular outcomes, especially in subjects previously free of CVD (HR 2.5; 95% CI 1.22-5.01). In this study it was also shown that subjects that had been prescribed gluten-free products had lower rates of CVD. This enhanced the tantalizing possibility that a GFD, which abolishes disease activity, may return the cardiovascular risk to normal (55).

In contrast to the already cited high prevalence of CD in idiopathic cardiomyopathy (45) and a few case reports of patients with cardiomyopathy associated with CD (56, 57), 2 studies, one from Italy and the other from Sweden, failed to identify a statistically significant association between CD, myocarditis, cardiomyopathy or pericarditis (58, 59).

TABLE I - CELIAC DISEASE AND CARDIOVASCULAR DISEASE RISK

Study	Participants (n)	Outcome measured	Results
Whorwell et al 1976 (44)	77 CD patients	Deaths from IHD compared with expected number of deaths from IHD	Protective p<0.05
Peters et al 2003 (50)	10032 CD patients 81182 controls	Mortality risk for CVD	SMR 1.6; 95% CI 1.40-1.80
West et al 2004 (18)	3790 CD patients 17925 controls	Risk of atrial fibrillation Risk of myocardial infarction Risk of stroke	HR 1.26; 95% CI 0.97-1.64 HR 0.85; 95% CI 0.63-1.13 HR 1.25; 95% CI 0.98-1.70
Ludvigsson et al 2007 (51)	13358 CD patients 64118 controls	Risk of myocardial infarction Risk of angina pectoris Risk of heart failure Risk of ischemic stroke	HR 1.27; 95% CI 1.09-1.48 HR 1.46; 95% CI 1.25-1.7 HR 1.41; 95% CI 1.22-1.62 HR 1.35; 95% CI 1.14-1.6
Wei et al 2008 (55)	367 CD patients 5537 controls	Risk of CVD in CD patients previously without CVD diagnosis	HR 2.5; 95% CI 1.22-5.01
Ludvigsson et al 2009 (52)	29096 patients Marsh 3 13306 patients Marsh 1-2 3719 patients latent CD	Risk of CVD in CD Marsh 3 Risk of CVD in CD Marsh 1-2	HR 1.19; 95% CI 1.11-1.28 HR 1.35; 95% CI 1.25-1.45
Godfrey et al 2010 (48)	127 undiagnosed CD 254 controls	Risk of cerebrovascular disease Risk of IHD	OR 0.99; 95% CI 0.45-2.21 OR 1.03; 95% CI 0.58-1.83
Canavan et al 2011 (49)	87 undiagnosed CD 7440 controls	Risk of CVD	HR 1.39; 95% CI 0.66-2.92
Emilsson et al 2011 (54)	28637 CD patients 141731 controls	Risk of atrial fibrillation	HR 1.34; 95% CI 1.24-1.44
Ludvigsson et al 2011 (53)	28190 patients Marsh 3 12598 patients Marsh 1-2 3658 patients latent CD	IHD mortality in CD Marsh 3 IHD mortality in CD Marsh 1-2	HR 1.22; 95% CI 1.06-1.40 HR 1.32; 95% CI 1.14-1.52
Ludvigsson et al 2011 (47)	29148 patients Marsh 3 13446 patients Marsh 1-2 3736 patients latent CD	Risk of stroke in CD patients: - compared with latent CD - compared with Marsh 1-2	 HR 1.35; 95% CI 1.01-1.79 HR 0.88; 95% CI 0.79-0.97

CD, celiac disease; HR, hazard ratio; IHD, ischemic heart disease; CVD, cardiovascular disease; SMR, standardized mortality ratio, OR, odds ratio

CD is more frequent in individuals with type 1 diabetes mellitus (T1DM) than in the general population (60). Therefore, the effect of comorbidity with T1DM and CD on cardiovascular risk factors is of importance. A study by Pitocco et al (61) measuring carotid intima-media thickness (CIMT), a surrogate marker for atherosclerosis, found that CIMT in patients with both CD and T1DM was significantly elevated compared with patients having isolated T1DM or CD, and compared with healthy controls. Furthermore, both patients with isolated CD or T1DM had significantly elevated CIMT compared with healthy controls (61). At the time of recruitment, all CD patients were following a GFD for at least 1 year, and all were in clinical, endoscopic and serological remission. These findings suggest that the association of CD and T1DM may accelerate the atherosclerotic process. In contrast, Picarelli et al (62) found a protective role for CD on the prothrombotic state of T1DM, as well as on the development of diabetic microvascular complications. In this study, a cohort of 13 patients affected by both T1DM and CD, not on GFD, were found to have significantly lower concentrations of glycosylated hemoglobin (6.5% ± 0.8 vs 7.4% ± 1.3; $p<0.05$), cholesterol (178 mg/dL ± 22.72 vs 239.5 mg/dL ± 35.7; $p<0.001$), triglycerides (96 mg/dL ± 30.7 vs 156 mg/dL ± 25.8; $p<0.001$), factor VII antigen

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(98.57% ± 33.11 vs 131.66% ± 21.69; p<0.005), factor VII coagulant activity (78.88 U/dL ± 14.99 vs 134.17 U/dL ± 50.28; p<0.05) and prothrombin degradation fragments (0.81 mmol/L ± 0.27 vs 1.49 mmol/L ± 0.59; p<0.001) than patients with isolated T1DM. Age and time interval from the diagnosis of diabetes were similar in patients in the 2 groups. In addition, no retinal abnormalities or signs of renal deterioration were observed in the group having both T1DM and CD. These thought provoking results, if reproduced in additional populations, raise intriguing questions about the necessity and even desirability of treating patients having both T1DM and CD with a GFD (62). Clearly, further studies are needed to replicate these findings in additional cohorts, as well as to identify what, if any, difference was caused by introduction of GFD in this (and other) cohorts of patients.

SUMMARY

In this brief review we have attempted to highlight the conflicting data regarding the relationship between CD, GFD and CVD. Overall, it remains difficult, with the currently available evidence, to clearly define how either CD or GFD affect the risk of developing CVD.

Two conflicting schools of thought exist that assign a role to GFD either as protective or as providing additive risk factors for the development of CVD. The hypothesis that GFD may be protective focuses on the fact that the introduction of GFD diminishes intestinal inflammation and, in addition, improves intestinal absorption. Concomitantly, several studies over the past decade have demonstrated that systemic markers of inflammation are increased in a large proportion of patients with acute coronary syndrome (63, 64) and that several clinical conditions, commonly characterized by a persistent low grade of inflammation, such as autoimmune disorders (65, 66), may confer a higher risk of cardiovascular events. As such, the effect of reduced intestinal inflammation by treatment with a GFD may play a role in decreasing the risk of CVD in CD patients.

Moreover, from a nutritional point of view, improvement of intestinal absorption may lead to normalization of the lipid profile, with a consequent increase in HDL-C (39). It may also lead to an increase in soluble vitamin absorption, which may result in a decrease in homocysteine levels in the blood (15).

On the other hand, some studies have shown that an unguided GFD may be associated with an unbalanced diet due to a higher fat intake (12). As reaffirmed in a recently published review, intake of saturated fatty acids increases the LDL-C concentration in plasma and has therefore been suggested to increase the risk of IHD (67). Furthermore, studies have shown that the effect of GFD in increasing weight and percentage of fat may be an additive risk factor for CVD in developed countries where the incidence of overweight and obesity are rising both in the general population and in CD patients. Thus, clear conclusions cannot be currently reached.

Conflict of interest statement: none declared.
Financial support: none.

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