Coeliac and cardiovascular disease: a possible relationship between two apparently separate conditions

Nicola Bernardi[1], Edoardo Sciatti[2], Edoardo Pancaldi[1], Fabio Alghisi[1], Andrea Drera[1], Raffaele Falco[1], Enrico Vizzardi[1]

[1]Cardiology Unit, ASST Spedali Civili, Brescia and Section of Cardiovascular Disease, Department of Surgical-Medical Specialties, Radiological Sciences and Public Health, University of Brescia; [2]Cardiology Unit 1, ASST Papa Giovanni XXIII, Bergamo, Italy

Abstract

Coeliac disease (CD) is an autoimmune condition with a high prevalence among general population and multisystemic involvement: a more complex scene than a merely gastrointestinal disease. Therefore, an early diagnosis and treatment with a gluten-free diet is mainly important to reduce mortality and comorbidities. Together with autoimmune diseases (as Hashimoto thyroiditis, insulin-dependent diabetes mellitus, autoimmune liver disease and connective tissue diseases), also an accelerated progression of atherosclerosis and a higher prevalence of heart disease have been reported in coeliacs. In the present paper we tried to collect from literature the emergent data on the probable relationship between coeliac and cardiovascular disease, focusing on pathophysiological bases of vascular injury. Data and opinions on the development of cardiovascular risk in patients with CD are conflicting. However, the major evidence supports the theory of an increased cardiovascular risk in CD, due to many mechanisms of myocardial injury, such as chronic malabsorption, abnormalities of intestinal permeability, and direct immune response against self-proteins. The conclusions that come from these data suggest the utility of a careful cardiovascular follow up in coeliac patients.

Correspondence: Dr. Edoardo Sciatti, Cardiology Unit 1, ASST Papa Giovanni XXIII, Bergamo, Piazza OMS 1, 24127 Bergamo, Italy.
Tel. +39.035.2673521.
E-mail: edoardo.sciatti@gmail.com

Key words: Coeliac disease; cardiovascular disease; left ventricle; endothelium; inflammation; diastolic dysfunction.

Contributions: NB, manuscript drafting; NB, EP, FA, AD, RF, literature search: ES, EV, manuscript finalization, supervision. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: Not applicable.

Informed consent: The manuscript does not contain any individual person's data in any form.

Received for publication: 5 July 2022.
Accepted for publication: 17 July 2022.

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2023; 93:2366
doi: 10.4081/monaldi.2022.2366

Introduction

Celiac disease is a disease due to a genetically determined gluten intolerance, with a prevalence of 1% in the general population, and much higher (8-20%) in the high-risk population (first degree relatives of celiac patients and patients with autoimmune diseases) [1,2].

Given the increase in frequency of atypical clinical presentations, celiac disease is now considered a multisystem disease, the diagnosis of which can involve any branch of medicine. The importance of an early diagnosis lies in the significant reduction of morbidity and mortality with a gluten-free diet. In general, the traditional clinical manifestation includes gastrointestinal disturbances, such as chronic diarrhoea, abdominal distension and pain, and sometimes malabsorption [3]. However, gastrointestinal symptoms may be absent or less pronounced in the most common so-called atypical presentations of the disease, in which systemic and/or specific extra-intestinal manifestations of organ damage prevail, such as anaemia, osteoporosis, short stature, infertility, neurological and cardiological problems and associated immune-mediated pathologies [2].

In celiac disease, regular ingestion of wheat, rye and barley induces inflammation mediated by T cells in the intestine, and an autoimmune response to self-proteins, especially to type 2 transglutaminases, with the production of anti-transglutaminase antibodies (anti-tTG) [4].

Chicco et al. have shown that a simple test to detect anti-tTG IgA antibodies can be used reliably for a rapid diagnosis of celiac

disease in a cardiology setting [5]. The mechanisms by which the altered immune response is not limited to the gastrointestinal system, but can involve different organs, are still to be clarified. What is certain is that many autoimmune diseases have been associated with celiac disease. In fact, Hashimoto's thyroiditis, insulin-dependent diabetes mellitus, autoimmune hepatitis and connective tissue diseases were all found more frequently in celiac patients than in the general population (Figure 1) [6].

Celiac disease and cardiovascular disease

Cardiac involvement, both idiopathic and of immunological origin, has also recently been associated with celiac disease. Accelerated progression of atherosclerotic plaque was observed in patients with immunological diseases [7,8]. In the literature there are conflicting opinions regarding the cardiovascular risk associated with celiac disease, and the association between the two conditions has not been definitively established. In some reports, the finding of celiac disease in patients with dilated cardiomyopathy was not clearly attributed to cause-and-effect relationships or to common pathogenetic mechanisms [9,10].

The mechanisms hypothesized as possible responsible for cardiac damage in celiac patients could be many: among them, in the first place, chronic malabsorption can determine the development of cardiomyopathy secondary to nutritional deficiencies; furthermore, intestinal permeability abnormalities can lead to increased systemic absorption of various luminal antigens or infectious agents that could cause myocardial damage through immune-mediated mechanisms [11]; finally, myocardial damage may be secondary to an immune response directed against an antigen that is present both in the myocardium and in the small intestine [8-12].

Systemic inflammation and heart failure with preserved ejection fraction

The pathophysiological mechanisms underlying heart failure with preserved ejection fraction (HFpEF) have yet to be fully understood; nevertheless, many hypotheses have been formulated. the inflammatory system certainly plays a leading role, in fact the presence of endothelial dysfunction and increased oxidative stress has been shown in patients with HFpEF. It is still unclear whether increased inflammatory activity may be a cause or a consequence of this disease.

The presence of endothelial dysfunction has been demonstrated in many pathologies characterized by a high inflammatory component (a characteristic common to coeliac disease); particularly in patients with Crohn's disease, COPD, lupus and psoriasis [13-18].

Dilatated cardiomyopathy

Curione *et al*. in a recent systematic review studied patients with dilated cardiomyopathy, showing a higher prevalence of celiac disease compared to the general population. In the follow-up of this subgroup of patients, an improvement in cardiac performance was also reported after the introduction of the gluten-free diet [8].

Chicco et al. selected three patients positive for anti-tTG or antiendomysium antibodies in a study of 104 patients with dilated cardiomyopathy; all had reduced left ventricular systolic function. Over the next 16 months of follow-up under gluten-free diet: six months after diagnosis, the patient with dilated cardiomyopathy and the worst ejection fraction (20%) underwent heart transplantation; the other two patients showed an improvement in systolic function (from 38% to 47% and from 46% to 60%, respectively). The repetitive ventricular arrhythmias of one of the two patients were also no longer recorded on Holter ECG controls. The gluten-free diet also improved anaemia and subjective fatigue [5].

Makhdoom and Randall recently presented the case of a patient with idiopathic dilated cardiomyopathy associated with celiac disease, who had a dramatic improvement in heart function after the introduction of the gluten-free diet and the disappearance of antiendomysium antibodies. In support of the relationship between the two conditions, in this patient the accidental ingestion of gluten was followed by the immediate decay of cardiac function. This observation therefore suggests a critical role of the gluten-free diet in improving systolic function in patients with idiopathic dilated cardiomyopathy [19].

Ischemic heart disease

Even around ischemic heart disease, the data in the literature are conflicting: numerous studies have reported a statistically significant increase in the risk of ischemic heart disease (IHD) in celiac patients, although two British studies have suggested a slight reduction in risk or a not significant association [20,21]. The increased risk of ischemic heart disease in the celiac patient cannot be explained by traditional cardiovascular risk factors: celiac patients generally have a lower body mass index (BMI) than the general population, and are less often affected by arterial hypertension. Furthermore, one study found that they were less likely to be heavy smokers [22-24].

Emilsson *et al*. have suggested that systemic inflammation

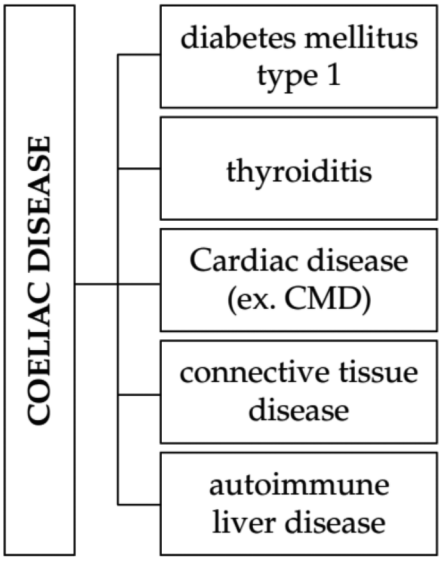

Figure 1. Frequent comorbidities in coeliac disease.

could be part of the mechanisms underlying the increased risk of ischemic heart disease. In their study of patients with myocardial infarction, C-reactive protein (CRP) tended to be higher (12%) in the celiac subgroup compared to controls, although the difference was not statistically significant [25].

Table 1 shows some studies on the association between celiac disease and cardiovascular disease. It also appears that celiac disease is associated with some of the most relevant cardiovascular risk factors, such as an altered lipid profile and an increased plasma level of homocysteine, the latter probably because of a vitamin deficiency. Fortunately, gluten deprivation appears to benefit the lipid profile by increasing plasma HDL levels in celiac patients [26,27]. De Marchi *et al*. in a study on patients with celiac disease and with a secondary increase in HDL-C concentrations in plasma, confirmed the beneficial effects of a gluten-free diet on the lipid profile [28].

Celiac disease atherosclerosis and cardiovascular damage

The increase in the median-intimal thickness (IMT) is an initial sign of atherosclerotic damage, which is associated with a series of cardiovascular risk factors such as diabetes, arterial hypertension, dyslipidaemia and autoimmune diseases [29]. The enhancement of the immune and inflammatory cascade are conditions related to endothelial damage, as well as causes of over-expression of cell adhesion molecules and production of reactive oxygen species. The cytokines, produced by inflammation, are involved in plaque formation and vascular damage; cytokine-mediated mechanisms are involved in both autoimmune disorders and cardiovascular damage. These conditions cause changes in the mid-intimal structure through an increase in collagen synthesis, cell population and lipid deposition.

The endothelium modifies its functions by depressing the synthesis of nitric oxide and/or increasing its demolition, with consequent reduction of the vasodilating capacity [30]. Figure 2 schematically represents the pathophysiology of vascular damage associated with celiac disease.

De Marchi *et al*. showed how the IMT is significantly increased in celiac patients, compared to healthy controls. The normalization of the mucosa of the small intestine following a gluten-free diet is associated with a return to normal of this parameter of early atherosclerosis. A reduced inflammatory response in celiac subjects following a gluten-free diet is also confirmed by the duodenal histology and by a significant decrease in the levels of C reactive protein (CRP) [28]. Based on the theory of the inflammatory genesis of atherosclerosis in immunological disorders [31], it could be hypothesized that this reduction in the inflammatory response may have beneficial effects on early atherosclerotic lesions in celiac disease.

Figure 2. Pathophysiology of vascular damage associated with coeliac disease.

Table 1. Characteristics of studies regarding coeliac disease and dilated cardiomyopathy.

Author, year	Study design	Patients	Cardiovascular disease evaluated and results
Chicco *et al.*, 2010 [5]	Case control	104 patients with DCM + 101 controls	DCM (higher incidence in coeliacs)
Vizzardi *et al.*, 2008 [9]	Case control	350 patients with DCM	DCM (similar incidence in coeliacs and general population)
Not *et al.*, 2003 [10]	Case control	230 patients with DCM, 2000 controls	DCM (higher incidence in coeliacs)
Curione *et al.*, 2002 [8]	Case report	3 patients with DCM	DCM (improvement in echocardiographic parameters aft glute free diet)
Makhdoom *et al.*, 2000 [19]	Case report	1 patient	DCM
Ludvigsson *et al.*, 2011 [21]	Cohort study	28,190 + 12,598 (low grade disease) + 3658 (latent coeliac disease)	DCM (higher mortality because of IHD in coeliacs)
West *et al.*, 2004 [22]	Case control	3790 coeliac patients + 17,925 controls	Cardiovascular mortality
Whorwell *et al.*, 1976 [23]	-	-	IHD (less mortality in coeliacs)
De Marchi *et al.*, 2013 [28]	Cohort study	20 coeliac patients	Atherosclerosis (early in coeliacs)
Emilsson *et al.*, 2012 [43]	Cohort study	29,000 patients	DCM (higher incidence in coeliacs)
Lebwohl *et al.*, 2017 [44]	Cohort study	64,714 women + 45,303 men without coeliac disease	IHD (non-associated with gluten free diet)

Diagnostic tools

From the diagnostic point of view, the early damage of cardiac function should be sought in patients with coeliac disease both for the purposes of clinical research and the confirmation of a relationship between the two pathologies and for a more effective therapeutic impact.

To this aim, an important technique to obtain evidence of subclinical damage of the ventricular function in patients with celiac disease and therefore to be able to undertake therapy early, could be the tissue doppler echocardiography (TDE). Polat *et al*. have shown that through traditional ultrasound and TDE, screening could be performed to search for early alterations in left ventricular function in patients with celiac disease. In the study there was a negative correlation between the AEA values and the mitral S wave (Sm) value at the TDE of all patients included in the study ($rn = -0.633$; $p<0.001$) [32].

Thus, TDE could contribute to early and correct identification of cardiac changes in patients with celiac disease. Furthermore, TDE appears normal in those patients with negative AEA, while significant disturbances of cardiac contractility are evident with the same method in patients with positive AEA. The evaluation of the systolic velocity peak of the mitral ring with TDE allows to estimate the systolic function of the left ventricle, like the parameters of the B-Mode or M-Mode echo, obtaining information that determines an estimate of the overall left ventricular systolic function [33,34].

Final evaluations

Patients with celiac disease have an increased risk of death, infectious disease and fractures [20,35]. Although death from CV causes is the most frequent in these patients, data regarding the correlation with ischemic heart disease are contradictory. Most, but not all studies have shown an increased incidence of IHD, death from IHD, or other cardiovascular diseases. Two studies conducted in Scandinavian countries have shown a significant increase in mortality secondary to cardiovascular diseases in celiac patients when compared to the general population [30,36]. Confirming this data, Peters et al. found that cardiovascular disease was the single most important cause of mortality, accounting for approximately 40% of all causes of death in coeliacs [37]. Data from a Scottish community-based cohort study demonstrate that composite cardiovascular risk appears to be increased in celiac disease with an increase of up to 2.5 [38]. In contrast to this evidence, a British population study revealed a different scenario: Whorwell *et al*. found that celiac disease patients had a 40% reduction in the development of life-threatening ischemic cardiovascular disease [23]. A recent study that evaluated 3,790 adult celiac patients from the General Practice Research Database of Nottingham (UK) did not demonstrate any significant increase in mortality from cardiovascular diseases, showing on the contrary a trend towards a reduced prevalence of ischemic heart disease in turn related to a minor prevalence of risk factors in this population. The authors think that the effect of a gluten-free diet can sometimes worsen the cardiovascular risk profile and therefore its impact in coeliac patients should be evaluated [22]. Finally, Heikkilä *et al*. found no clear evidence that undiagnosed celiac disease could have a marked incidence of coronary artery disease or heart disease [36]. The role and the prevalence of risk factors for atherosclerotic diseases in patients with celiac disease is not easily interpreted. While it is true that some reports highlight an improvement in the lipid profile following a gluten-free diet, other evidence points out that patients who follow this diet often do not take an adequate and balanced intake of fats, carbohydrates and fibres and this condition can contribute to the development of atherosclerosis. On the other hand, it is also possible that celiac disease, especially if not treated, can induce malabsorption of nutrients in the small intestine and consequently low concentrations of cholesterol, so as to reduce the risk of cardiovascular events [39-41]. In fact, some studies show that celiac patients smoke less and have a lower body mass index and lower cholesterol levels, but their blood pressure and CRP levels are similar to non-coeliac patients [23,25,37,42].

Ludvigsson *et al*. found an association between CD and IHD, confirming a possible association between inflammatory/autoimmune diseases and IHD [21]. In consideration of the fact that cardiovascular diseases are the most common cause of death in patients with chronic inflammatory diseases, this finding may have important implications in patients with CD. In fact, gluten acts as a trigger for inflammation and intestinal damage in patients with CD. It is suggestive that tissue transglutaminase (tTG), which is the main autoantigen in celiac disease, promotes angiogenesis, and that, on the contrary, anti-tTG antibodies, present in celiac patients, can inhibit it. This aspect could also be considered in the mechanisms of cardiovascular damage. However, the association between celiac disease and coronary heart disease remains controversial, although the evidence seems to suggest a reduction in risk after a period of gluten-free diet. Celiac patients who suffer from myocardial infarction very often do not have the classic cardiovascular risk factors [20,21], such as dyslipidaemia and smoking, reinforcing the hypothesis that the pro-inflammatory effect exerted by gluten is an independent risk factor. In recent years there has been a tendency in the population to follow low or gluten-free diets [25].

Although the evidence that gluten plays a role in the development of cardiovascular disease is still limited, the adoption of the gluten-free diet by patients without celiac disease has progressively led to the idea that gluten can have a deleterious effect. on health even in the absence of a sensitivity to gluten. The rationale for this concept is based on the high glycaemic index of foods that contain gluten, which may in fact be related to cardiovascular risk. Inflammation could also play a role in the pathogenesis of idiopathic dilated heart disease. Emilsson *et al*. found a moderate but not statistically significant increase in the risk of developing idiopathic dilated cardiomyopathy in patients with celiac disease; their results suggest that the two diseases may have the same aetiology or that inflammation in a patient who has not yet been diagnosed with celiac disease may act as a trigger for dilated cardiomyopathy [43]. However, it should be noted that Lebwohl *et al*. noted an inverse relationship between gluten intake and coronary heart disease when the intake is given by refined wheat in non-celiac adults [44].

Conclusions

Ultimately there are contradictory results and conflicting interpretations on the prevalence of CV risk factors over theirs etiopathogenetic mechanisms and CV events in celiac patients: these discrepancies could probably be attributed at least in part to the difference in the design of the studies, the different method of data collection and the frequent low number of samples analysed. It would be advisable to design studies with adequate numbers and follow-ups to try to definitively clarify these relationships. Although the role of celiac disease as a cardiovascular risk factor

still includes many aspects to be clarified, several possible pathophysiological pathways of celiac disease-induced vascular damage have been highlighted. In the current state of knowledge, celiac patients, as potentially chronically exposed to this damage, should be followed up with cardiological follow-up both as regards exposure to risk factors and as regards early organ damage through methods. of simple approach such as echocardiography.

References

1. Tommasini A, Not T, Kiren V, et al. Mass screening for coeliac disease using antihuman transglutaminase antibody assay. Arch Dis Child 2004;89:512-5.
2. Green P, Cellier C. Celiac disease. N Engl J Med 2007;357: 1731-43.
3. Corrao G, Corazza GR, Bagnardi V, et al; Club del Tenue Study Group. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358:356-61.
4. Koning F. Celiac disease: caught between a rock and hard-place. Gastroenterology 2005;129:1294-301.
5. Chicco D, Taddio A, Sinagra G, et al. Speeding up coeliac disease diagnosis in cardiological settings. Arch Med Sci 2010; 6,5:728-32.
6. Fasano A. Systemic autoimmune disorders in celiac disease. Curr Opin Gastroenterol 2006;22:674-9.
7. Frustaci A, Cuoco L, Chimenti C, et al. Celiac disease associated with autoimmune myocarditis. Circulation 2002;105: 2611-8.
8. Curione M, Barbato M, Viola F, Francia P, De Biase L, Cucchiara S. Idiopathic dilated cardiomyopathy associated with coeliac disease: the effect of a gluten-free diet on cardiac performance. Dig Liver Dis 2002;34:866-9.
9. Vizzardi E, Lanzarotto F, Carabellese N, et al. Lack of association of coeliac disease with idiopathic and ischaemic dilated cardiomyopathies. Scand J Clin Lab Invest 2008;68:692-5.
10. Not T, Faleschini E, Tommasini A, et al. Celiac disease in patients with sporadic and inherited cardiomyopathies and in their relatives. Eur Heart J 2003;24:1455-61.
11. DeMeo MT, Mutlu EA, Keshavarzian A, Tobin MC. Intestinal permeation and gastrointestinal disease. J Clin Gastroenterol 2002;34:385-96.
12. Chimenti C, Pieroni M, Maseri A. Dilated cardiomyopathy and celiac disease. Ital Heart J 2002;3:385.
13. Sciatti E, Orabona R. A window of opportunity on cardiovascular prevention: pre-eclampsia and fetal growth restriction. Eur J Prev Cardiol 2022;28:e17-8.
14. Cavazzana I, Piantoni S, Sciatti E, et al. Relationship between endothelial dysfunction, videocapillaroscopy and circulating CD3+CD31+CXCR4+ lymphocytes in systemic lupus erythematosus without cardiovascular risk factors. Lupus 2019;28:210-6.
15. Gorga E, Scodro M, Valentini F, et al. Echocardiographic evaluation of diastolic dysfunction in young and healthy patients with psoriasis: A case-control study. Monaldi Arch Chest Dis 2018;88:934.
16. Malerba M, Radaeli A, Nardin M, et al. Endothelial dysfunction assessment by noninvasive peripheral arterial tonometry in patients with chronic obstructive pulmonary disease compared with healthy subjects. Clin Respir J 2018;12:1466-72.
17. Vizzardi E, Sciatti E, Bonadei I, et al. Subclinical cardiac involvement in Crohn's disease and ulcerative colitis: an echocardiographic case-control study. Panminerva Med 2016;58:115-20.
18. Sciatti E, Orabona R. A still-ignored cardiovascular risk factor-A history of preeclampsia. JAMA Cardiol 2021;6:1097-8.
19. Makhdoom ZA, Randall NW. Dilated cardiomyopathy due to anticardiolipin syndrome in association with celiac sprue. J Clin Gastroenterol 2000;31:91-2.
20. Ludvigsson J, Montgomery SM. Small intestinal histopathology and mortality risk in celiac disease. JAMA 2009;302: 1171-8.
21. Ludvigsson JF. Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. Circulation 2011;123:483-90.
22. West J, Logan RF, Card TR, Smith C, Hubbard R. Risk of vascular disease in adults with diagnosed celiac disease: a population-based study. Aliment Pharmacol Ther 2004;20:73-9.
23. Whorwell PJ. Death from ischaemic heart disease and malignancy in adult patients with coeliac disease. Lancet 1976;2:113-4.
24. Snook JA. Adult coeliac disease and cigarette smoking. Gut 1996;39:60-2.
25. Emilsson L. The characterization and risk factors of ischemic heart disease in patients with coeliac disease. Aliment Pharmacol Ther 2013;37:905-14.
26. Brar P, Kwon GY, Holleran S, et al. Change in lipid profile in celiac disease: beneficial effect of a gluten-free diet. Am J Med 2006;119:786-90.
27. Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in celiac patients on a gluten-free diet for 10 years. Aliment Pharmacol Ther 2006;16:1333-9.
28. De Marchi S, Chiarioni G, Prior M, Arosio E. Young adults with coeliac disease may be at increased risk of early atherosclerosis. Aliment Pharmacol Ther 2013;38:162-9.
29. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common carotid intima-media thickness and arterial stiffness: indicator of cardiovascular risk in high-risk patients. The SMART Study. Circulation 1999;100:951-7.
30. Viljama M, Kaurinen K, Pukkala E. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: a 30-year population-based study. Dig Liv Dis 2006;38:374-80.
31. Szucs G, Tímár O, Szekanecz Z, et al. Endothelial dysfunction precedes atherosclerosis in systemic sclerosis relevance for prevention of vascular complication. Rheumatology 2007;46: 759-62.
32. Tugcin B, Nafiye U, Yalim Y, et al. Cardiac functions in children with coeliac disease during follow-up: Insights from tissue Doppler imaging. Dig Liver Dis 2008;40:182-7.
33. Henry WL, Bonow RO, Rosing DR, Epstein SE. Observation on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic Evaluation of asymptomatic patients. Circulation 1980;61:484-92.
34. Waggoner AD, Bierig SM. Tissue Doppler imaging: a useful echocardiographic method for the cardiac sonographer to assess systolic and diastolic ventricular function. J Am Soc Echocardiogr 2001;14:1143-52.
35. West J, Logan RF. Fractures risk in people with celiac disease: a population-based cohort study. Gastroenterology 2003;125: 429-36.
36. Heikkilä K, Koskinen OA, Agarwal A, et al. Associations of coeliac disease with coronary heart disease and cerebrovascular disease: A systematic review and meta-analysis. Nutr Metab Cardiovasc Dis 2015;25:816-31.

37. Peters U, Askling J, Gridley G, et al. Causes of death in patients with celiac disease in a population based Swedish cohort. Arch Intern Med 2003;163:1566-72.
38. Wei L, Spiers E, Reynolds N, et al. Association between celiac disease and cardiovascular disease. Aliment Pharmacol Ther 2008;27:514-9.
39. Dickey W. Overweight in celiac disease: prevalence, clinical characteristics, and effect of gluten-free diet. Am J Gastroenterol 2006;101:2356-9.
40. Wild D. Evidence of high sugar intake, and low fibrate and mineral intake, in the gluten free diet. Aliment Pharmacol Ther 2010;32:573-81.
41. Kim HS, Patel KG. Time trends in the prevalence of celiac disease and gluten free diet in the US population: results from the National Health and Nutrition Examination Surveys 2009-2014. JAMA Intern Med 2016;176:1716-7.
42. Sciatti E, Bernardi N, Dallapellegrina L, et al. Evaluation of systo-diastolic cardiac function and arterial stiffness in subjects with new diagnosis of coeliac disease without cardiovascular risk factors. Intern Emerg Med 2020;15:981-8.
43. Emilsson L, Andersson B, Elfström P, et al. Risk of idiopathic dilated cardiomyopathy in 29 000 patients with celiac disease. J Am Heart Assoc 2012;1:e001594.
44. Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. BMJ 2017;375:j1892.