Setare Akbari

Abstract

Celiac disease (in English: Celiac disease) or celiac sprue is an allergic and autoimmune disorder of the small intestine with a genetic (hereditary) background. In this digestive disease, the villi of the small intestine are damaged and the absorption of substances is impaired. .
Celiac disease (CD) is a chronic immune-mediated disorder with multiple extraintestinal manifestations. The increased incidence of cardiac morbidities in celiac patients highlights the importance of early detection of sub clinical myocardial dysfunctions. In this study, we aimed to assess the cardiac functions and explore early subclinical myocardial dysfunctions in celiac patients by tissue Doppler imaging.

Keywords: Celiac disease, Myocardial dysfunction, Tissue Doppler echo, Echocardiography

1.Introduction

Coeliac disease (British English) or celiac disease (American English) is a long-term autoimmune disorder, primarily affecting the small intestine, where individuals develop intolerance to gluten, present in foods such as wheat, rye and barley. Classic symptoms include gastrointestinal problems such as chronic diarrhoea, abdominal distention, malabsorption, loss of appetite, and among children failure to grow normally. Non-classic symptoms are more common, especially in people older than two years. There may be mild or absent gastrointestinal symptoms, a wide number of symptoms involving any part of the body, or no obvious symptoms. Coeliac disease was first described in childhood; however, it may develop at any age. It is associated with other autoimmune diseases, such as Type 1 diabetes mellitus and Hashimoto's thyroiditis, among others.

Coeliac disease is caused by a reaction to gluten, a group of various proteins found in wheat and in other grains such as barley and rye. Moderate quantities of oats, free of contamination with other gluten-containing grains, are usually tolerated. The occurrence of problems may depend on the variety of oat. It occurs more often in people who are genetically predisposed. Upon exposure to gluten, an abnormal immune response may lead to the production of several different autoantibodies that can affect a number of different organs. In the small bowel, this causes an inflammatory reaction and may produce shortening of the villi lining the small intestine (villous atrophy). This affects the absorption of nutrients, frequently leading to anaemia. Diagnosis is typically made by a combination of blood antibody tests and intestinal biopsies, helped by specific genetic testing. Making the diagnosis is not always straightforward. About 10% of the time, the autoantibodies in the blood are negative, and many people have only minor intestinal changes with normal villi. People may have severe symptoms and they may be investigated for years before a diagnosis is achieved. As a result of screening, the diagnosis is increasingly being made in people who have no symptoms. Evidence regarding the effects of screening, however, is not sufficient to determine its usefulness. While the disease is caused by a permanent intolerance to gluten proteins, it is distinct from wheat allergy, which is much more rare.

The only known effective treatment is a strict lifelong gluten-free diet, which leads to recovery of the intestinal lining (mucous membrane), improves symptoms, and reduces the risk of developing complications in most people. If untreated, it may result in cancers such as intestinal lymphoma, and a slightly increased risk of early death. Rates vary between different regions of the world, from as few as 1 in 300 to as many as 1 in 40, with an average of between 1 in 100 and 1 in 170 people. It is estimated that 80% of cases remain undiagnosed, usually because of minimal or absent gastrointestinal complaints and lack of knowledge of symptoms and diagnostic criteria. Coeliac disease is slightly more common in women than in men.

Signs and symptoms

The classic symptoms of untreated coeliac disease include pale, loose, or greasy stools (steatorrhoea), and weight loss or failure to gain weight. Other common symptoms may be subtle or primarily occur in organs other than the bowel itself. It is also possible to have coeliac disease without any of the classic symptoms at all. This has been shown to comprise at least 43% of presentations in children. Further, many adults with subtle disease may only present with fatigue, anaemia or low bone mass. Many undiagnosed individuals who consider themselves asymptomatic are in fact not, but rather have become accustomed to living in a state of chronically compromised health. Indeed, after starting a gluten-free diet and subsequent improvement becomes evident, such individuals are often able to retrospectively recall and recognise prior symptoms of their untreated disease that they had mistakenly ignored.

3.The history of echocardiography

During the 1930s and 1940s, the application of ultrasound for medical therapeutic purposes was widespread. In Germany, Austria, France and Switzerland, it was used for a variety of diseases, especially neuralgia, myalgia, arthritis and arthrosis, for which heat was considered beneficial (Pohlmann 1951). Some doctors with an interest in technology came up with the idea to use ultrasound for medical diagnostic purposes. They were inspired by the knowledge of the use of ultrasound for echo-sounding the depth of the ocean (Behm 1921), as well as the detection of flaws in materials or constructions suggested by Sokoloff in 1929 (Sokoloff 1929), described by Sokoloff in 1935 Sokoloff 1935a, Sokoloff 1935b and solved by Sproule in England in 1944 (Wells 1969) and Firestone in the USA in 1945 (Firestone 1945).

In 1940, Gohr and Wedekind (1940) suggested the use of reflected ultrasound for the detection of tumours, exudates, abscesses and so on. They also worked practically on the problem, but never published any results.

The French physiotherapist Denier 1946a, Denier 1946b proposed that ultrasound might be used to produce images of interior body structures. His idea was as follows: a sound beam was transmitted through the body and picked up by a second quartz crystal working at the same frequency as the generator. The received signals were to be displayed on an oscilloscope wired to display Lissajous figures. In this manner he would be able to locate and estimate the shape of the heart, spleen, liver and stomach. Pathologic structures also could be identified. However, he apparently failed in the construction of the instrumentation that he envisioned.

3.2.Section snippets

The first use of reflected ultrasound as a medical diagnostic tool

The efforts of the Austrian neurologist Karl Theo Dussik (Fig. 1) were not more successful. He worked with his brother, physicist Frederick Dussik, using the transmission method for producing an image based on the differential attenuation of sound during its passage through the head (Dussik 1942). In 1947, after almost a decade of work, Dussik could produce ultrasonically generated images, "hyperphonograms," of what he believed to be the ventricles of the brain (Dussik et al. 1947). The first

Ultrasound investigation of the thorax

In the mid 1940s, German physician Wolf-Dieter Keidel (Fig. 6), working at Physikalisch-Medizinischen Laboratorium at the University in Erlangen, Germany, studied the possibility of using ultrasound as a medical diagnostic tool. In 1950, he described a new ultrasonic method for recording the rhythmic volume variations of the heart (Keidel 1950).

The method arose as a result of earlier attempts to quantify the clinical routine method of percussion. Percussion was introduced in 1761 by the

Reflected ultrasound

Both Dussik and Keidel eliminated the possibility of using reflected ultrasound for theoretical reasons; therefore, they never performed any practical experiments with reflected ultrasound.

The first report of the practical use of this method came in 1949 from Ludwig and Struthers (1949), who attempted to detect gallstones and foreign bodies buried in the muscles of dogs. They used the principle of ultrasonic flaw detection in materials described by Firestone (1945). Very short pulses of

What was the object of receiving echoes from heart structures?

In May 1953, Inge Edler (Fig. 11a) and C. Hellmuth Hertz (Fig. 11b) met to discuss the possibilities of using ultrasound for heart investigation. The meeting was arranged by the physicist Jan Cederlund, whom Edler had asked about the possibilities of using ultrasound or radar for diagnosing mitral regurgitation. Why mitral regurgitation? The reason was that, in the early 1950s, before the introduction of left ventricular angiocardiography, there was no method for the exact diagnosis of this

The first use of ultrasound in clinical routine

In 1954, echocardiography was used in Lund as a routine clinical application for diagnosis and follow-up studies of pericardial effusion. This was the first clinical application of diagnostic ultrasound. Follow-up studies of six cases were presented at the scientific session held by The Swedish Society of Internal Medicine in Lund on 4 June 1955 (Edler 1955a; Fig. 30). As the equipment had no facilities for "time-gain-compensation," only the anterior part of the heart was investigated in cases

Echocardiography as a diagnostic tool: 1954–1960

At the Third European Congress in Cardiology in Rome 1960, Edler, Gustafson, Karlefors and Christensson presented a scientific film describing the echocardiographic technique and the clinical application of the method (Edler et al. 1960a). The most important use of echocardiography at this time was in patients with pericardial effusion or mitral stenosis. In 1960, more than 300 patients with mitral valve disease had been investigated. In pure mitral stenosis, the anterior mitral leaflet had a

Echocardiography outside lund

Director Gellinek at the Siemens-Reiniger Werke in Erlangen was interested in introducing echocardiography in West Germany. Therefore, Hertz, during his stay in Erlangen in 1956–1957,

stimulated doctors from three different centres (the medical departments in Düsseldorf, Hamburg and Würzburg) to use the method. Doctors from these three centres were sent to Lund to learn the examination technique and subsequent clinical evaluation of the results. The most successful was Doctor Sven Effert from

Introduction of echocardiography in the USA

In 1956, Rushmer et al. (1956) presented a technique for measuring left ventricular dimensions in intact dogs by using ultrasound sonocardiometry. Two small discs of barium titanate were sutured to the external surface of the cardiac wall on opposite sides of a chamber. One of the crystals served as transmitter, and short pulses, 1 μs, were transmitted. The time required for the sound wave to pass through the chamber to the receiver crystal on the opposite side is continuously monitored 1000 to

The clinical application of echocardiography during the 1960s

The main application of echocardiography during the 1960s was for the evaluation of mitral valve disease. Several groups of investigators reported a good correlation between the reduction in speed of the diastolic downstroke E-F and the degree of stenosis Buhr et al 1967, Effert 1959, Effert 1967, Edler 1961, Edler 1966, Edler 1967, Reid and Joyner 1965, Joyner and Reid 1965, Gustafson 1966, Gustafson 1967, Segal et al 1966. Effert reported his experience of 3076 patients with mitral valve

Mitral stenosis after closed commissurotomy: Echocardiographic long-term follow-up

From the beginning, echocardiography had a large impact on the diagnosis and assessment of mitral valve stenosis. As mentioned earlier, a reduced rate of anterior mitral leaflet closure (E-F slope) is the classic criterion for the echocardiographic diagnosis of mitral stenosis (Edler 1955b). The relationship between the E-F slope and mitral valve area assessed at cardiac catheterisation and surgery was described in several reports from the 1960s Edler 1967, Gustafson 1966, Joyner et al 1963a,

The first commercial equipment

In the mid 1960s, the stage was set for the commercialisation of the ideas into special purpose equipment. Up to that time, the Swedish and German groups had been forced to use industrial flaw detection devices. The Pennsylvania group was the only one with specially developed equipment. In the USA, commercialisation proceeded through a parallel effort by the Sonomedic Corporation and the Smith-Kline French Corporation. The Sonomedic Corporation was the first to produce a machine in pilot

The continuing development of echocardiography in the USA

William L. Winters Jr. of the Division of Cardiology, Temple Medical School in Philadelphia, was invited in 1962 by Claude Joyner to see the work performed at his laboratory. Winters was very impressed, and shortly thereafter he obtained a Sperry ultrasound machine and an early Smith-Kline ultrasound machine. In 1963, Winters began working with ultrasound together with Jose Gimenez of the Department of Radiology, Temple Medical School. They began using the ultrasound equipment as a clinical

Contrast echocardiography

The echocardiography anatomy described by Edler and associates Edler 1961, Edler 1965, Edler et al 1960b was confirmed and completed by Gramiak and coworkers in 1968–1972. On 28 April 1967, a young man was being studied for aortic regurgitation in the cardiac catheterisation laboratory. An

echocardiogram performed during left ventricular injection of indocyanine-green revealed dense contrast filling the cavity, with a defect in the pattern produced by noncontrast blood through the mitral

Two-dimensional echocardiography

Before 1965, the interest in echocardiography was very slight, even though, according to Feigenbaum (1976), the M-mode technique had the capability of displaying cardiac motion in a method not available by almost any other diagnostic procedure including angiocardiography. The main reason for this was that most doctors were not able to understand the M-mode records. They could not relate the records to anatomical stuctures of the heart because they did not have the faculty of seeing in three

The lund real-time cardiac scanners

In the late 1950s, Hertz and Edler often discussed the possibility of producing two-dimensional images of the heart. In the previously developed two-dimensional cross-sectional imaging, the transducer was moved at a slow rate in the area over the organ to be visualised (Baum and Greenwood 1958, Donald and Brown 1961, Donald et al 1958, Holmes and Howry 1954, Howry and Bliss 1952, Howry et al 1954; Wild and Reid 1952). This method is impossible to use for heart investigations, since the

Early Japanese investigations in two-dimensional echocardiography

Inspired by the investigations with two-dimensional ultrasound images of soft tissues reported by Wild and Reid and Howry and Bliss, the Japanese investigators Kikuchi, Wagai and coworkers started using ultrasound and presented similar two-dimensional pictures of the brain, abdomen and breast tumours. They used plan-position indication (PPI), B-scope indication and time-position indication (TPI). A barium titanate transducer working at a frequency of 1 MHz was used. Kikuchi and coworkers named

The stop-action images

The stop-action technique for cardiac ultrasonography was described by Donald L. King in 1970 (King 1972). He became interested in ultrasound when, as a resident in radiology, he saw in a popular magazine an article about the work of Howry and Holmes at Colorado University, Denver, CO, USA. The article showed the famous “cross-section of the neck,” visualising the carotid artery, jugular vein and vagus nerve (Fig. 102). For King, it was immediately obvious from those images that this new

Linear array system

In 1971, Nicolaas Bom in The Netherlands presented the first real-time linear array used to obtain moving cardiac images. After finishing high school, Bom was not sure what to study, and he flipped a coin to decide between medical study and study for electronic engineering. Fate decided that he went to the University of Technology at Delft. After his examination, he served duty as a naval officer for 2 years. He was active in a sonar laboratory and subsequently moved to a NATO sonar laboratory

Ultrasound in paediatric and congenital heart disease

The first attempt to use ultrasound for diagnosing congenital heart disease was made by Gässler in Hamburg, Germany. Together with Jacobi and Samlert in 1958, she published a report of 40 patients with left-to-right shunts investigated using reflected ultrasound (Jacobi et al. 1958). In 17 of 18 patients with atrial septal defect, they considered the movement pattern of the anterior mitral leaflet to be abnormal. However, this “abnormality” was due to tachycardia. The A-waves started

The Doppler effect: Theory and experimental verification

In May 25 1842, at a meeting of the Royal Bohemian Society of Sciences in Prague, Christian Doppler presented his paper, “Über das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels” (“On the coloured light of double stars and some other stars on the heaven”). This paper was published the following year in *Abhandlungen der Königlichen Böhmischen Gesellschaft der Wissenschaften* (Doppler 1843). A copy of the title page is shown in Fig. 136. Changes in wavelength of light

Dr. Inge Edler died on 7 March 2001, ten days short of his ninetieth birthday.

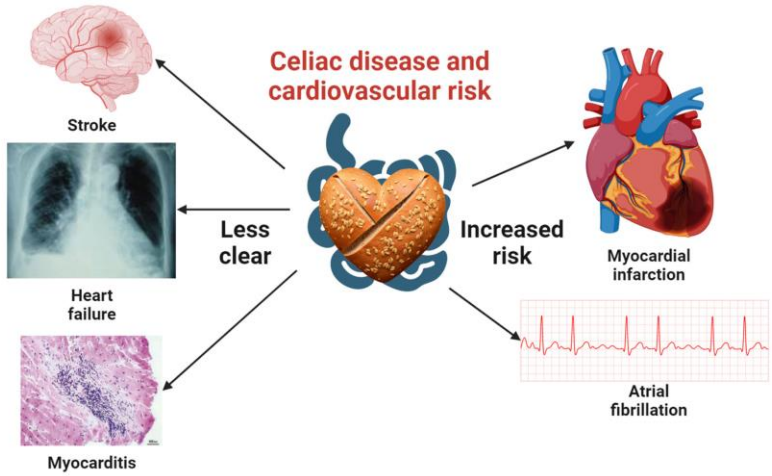

Fig 1. Comprehensive visualization of the association between celiac disease and cardiovascular disease risk. This central illustration highlights the well-documented links between celiac disease, Figure 1. Comprehensive visualization of the association between celiac disease and cardiovascular disease risk. This central illustration highlights the well-documented links between celiac disease, myocardial infarction, and atrial fibrillation. It also emphasizes the need for additional studies to clarify the connections with stroke, heart failure, and myocarditis. Icons representing myocardial infarction, atrial fibrillation, and stroke were obtained from Biorender.com, while those for heart failure and myocarditis were sourced from open-access articles on PubMed Central, identified through an Open-i search . A heart-shaped barley bread icon, created using the Stable-Diffusion text-to-image model, signifies the context of celiac disease in this investigation. myocardial infarction, and atrial fibrillation. It also emphasizes the need for additional studies to clarify the connections with stroke, heart failure, and myocarditis. Icons representing myocardial infarction, atrial fibrillation, and stroke were obtained from Biorender.com, while those for heart failure and myocarditis were source dfromopen- accessarti cleson PubMed Central, identified through an Open-i search. A heart-shaped barley bread icon, created using the Stable-Diffusion text-to image model, signifies the context of celiac disease in this investigation. Two meta-analyses published in 2015 analyzed evidence predat

4. Material and methods

This is a cross-sectional study in which 78 children aged between 6 months and 18 years were included. They were enrolled over a period of 6 months from December 2021 to May 2022 at Cairo University Children Hospital. They were divided into two groups; group 1 included 42 patients with celiac disease (24 females and 18 males), following up in the gastroenterology out patient clinic of Cairo University Children Hospital. Diagnosis was confirmed by clinical data, serology, and esophagogastroduodenoscopy with biopsy, after exclusion of patients with other gastrointestinal illnesses, congenital or acquired heart diseases, and additional systemic illnesses, e.g., diabetes mellitus and autoimmune thyroiditis. And group 2 included 36 healthy, age- and sex-matched children (18 males and 18 females) without gastrointestinal or cardiac problems as a control group. The study was approved by Higher studies Research Committee of Faculty of Medicine Cairo University. Oral informed consent was obtained from the legal guardians. For all patients who met the inclusion criteria, full medical history was taken with special emphasis on gastrointestinal manifestations, extraintestinal findings, cardiac symptoms, and dietary compliance that

was evaluated 6 months after adequate diet control (strict gluten-free diet). Comprehensive physical examination was done including anthropometric measurements, vital signs including HR, RR, and BP; full abdominal examination; and cardiac examination. The patients' files were revised for the results of antibody titers: anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA) and immunoglobulin G (IgG), total IgA, anti-endomysial (EMA) antibody IgA, anti-gliadin (DGP) antibody IgA and IgG, CBC and iron profile, upper endoscopy, and biopsy. For each participant, full transthoracic echocardi ography (TTE), with experienced pediatric cardiologist, was carried out using a General Electric Vingmed Ultrasound System (Vivid E95) with 6S and M5Sc probes, according to the recommendations of the American Society of Echocardiography . The following were measured by conventional echocardiography:

1. M-mode measurements including fractional shorten ing (FS), ejection fraction (EF)

2. Pulsed Doppler echocardiography to measure: Peak early diastolic filling velocity (E wave), peak late dias tolic velocity (A wave), early to late diastolic flow ratio (E/A), deceleration time (DT) for both mitral (MV) and tricuspid valves (TV) By tissue Doppler imaging, we assessed the following: systolic myocardial velocities at the basal segments of the lateral, septal, and anterior walls (S) as well as early and late diastolic myocardial velocities and their ratios (E′, a′, and E′/a′, E/e′ respectively). Myocardial performance index (MPI) of both ventricles was calculated as follows: MPI = (a − b)/b, the normal MPI index for LV and RV are 0.32 ± 0.07 and 0.27 ± 0.09, respectively (Fig. 1). For all measures, the mean of three cardiac cycles was taken.

Statistical analysis

Data were coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. The comparison between groups regarding qualitative data was done by using chi-square test and/or Fisher's exact test when the expected count in any cell found less than 5. The com parison between two independent groups with quantitative data and parametric distribution was done by using independent t-test while with non-parametric distribution was done by using Mann–Whitney test. The com parison between two paired groups regarding quantitative data and parametric distribution was done by using paired t-test while with non-parametric distribution was done by using Wilcoxon rank test. The comparison between more than two groups regarding quantitative data and para metric distribution was done by using one-way ANOVA test while with non-parametric distribution was done by using Kruskal–Wallis. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: non significant (NS), P-value < 0.05: significant (S), P-value < 0.01: highly significant (HS).

5.Results

This is a cross-sectional analytic study that was conducted on 78 children, at Cairo University Children Hospital, over a period of 6 months. They were divided into two groups: 42 patients who were diagnosed with celiac disease before enrollment in the current study, and 36 age- and sex matched controls. The patients were evaluated 6 months after strict diet control (gluten-free diet). The demo graphic data of included cases and controls regarding age, sex, and family history and BP are shown in Table 1. Our

patients had significantly lower weight, height, and BMI in relation to the controls. They had significantly higher SPB and significantly lower DBP than the controls.

Table1. Clinico-demographic data of studied groups

Demographic data	Cases ($n=42$) Mean ± SD	Controls ($n=36$) Mean ± SD	*P* value
Age (years)	8.8 ± 3.8	8.2 ± 3.8	0.183
Males	18 (42.9%)	18 (50.0%)	0.528
Females	24 (57.1%)	18 (50.0%)	
Family history (+ve)	4 (9.5%)	0 (0.0)	0.057
Weight (kg)	26.0 ± 12.6	27.88 ± 8.74	0.001
Height (cm)	121.6 ± 17.2	123.96 ± 10.24	0.049
BMI (km/m$^{2)}$	16.7 ± 3.8	17.12 ± 2.3	0.001
SBP (mmHg)	107.5 ± 14.5	102.5 ± 4.6	0.035
DBP (mmHg)	66.3 ± 13.6	73.8 ± 3.3	0.001

The most prominent abdominal complaints in our patients were abdominal distention (65.9%) followed by chronic diarrhea (63.4%). The most prominent extraintestinal manifestations were failure to thrive (50%), iron deficiency anemia (42.9%0), short stature (30.9%), and behavioral changes/insomnia/fatigue (14.3%). Twenty six (61.9%) patients had positive serology. All our patients had done endoscopy and biopsy to confirm the diagnosis. Forty (95.2%) children were strict to gluten-free diet (GFD) while 2 (4.8%) children were incompliant as registered in their files. As regards M mode measurements of our patients, they are shown in Table 2. As enlisted in Table 2, our patients had dilated aorticroot and dilated RV in relation to controls. LV was dilated but not to a significant level. Results of conventional pulsed Doppler are shown in Table 3. As seen in Table 3, the patients had significantly lower E/A ratio of tricuspid valve and higher E/A ratio of mitral valve in relation to controls. As shown in Table 4, our patients had significantly lower mitral E′/a′ and higher tricuspid E′/e′ when com pared to controls. There was statistically significant longer MPI of RV in patients than controls. Yet biventricular MPI were within normal limits. As shown in Table 5, there are statistically significant lower E′/a′ ratio of the tricuspid and mitral valves in patients with extra intestinal manifestations ($p = 0.041$, $p = 0.009$ respectively)

Table 2. M-mode measurements of patients and controls

Conventional echocardiographic measurements	**Cases ($n = 42$)**	**Controls ($n = 36$)**	***P* value**
M-mode parameters (mm)	**Mean ± SD**	**Mean ± SD**	
AO	25.9 ± 3.24	17.62 ± 2.91	**0.027**
LA	21.69 ± 3.62	18.6 ± 2.99	0.286
RV	20.13 ± 5.57	12.74 ± 3.44	**< 0.001**
IVST	5.55 ± 2.4	5.7 ± 1.98	0.234
LVPWT	5.38 ± 1.29	5.4 ± 2.22	0.186
LVEDd	39.5 ± 4.87	34.8 ± 3.67	0.143
LVESd	24.95 ± 3.73	20.7 ± 2.54	0.314
FS %	36.81 ± 5.15	37.52 ± 4.25	0.915
EF	67.07 ± 6.26	70.48 ± 3.33	0.362

6.discussion

Celiac disease is an autoimmune disorder affecting young children with wide range of manifestations ranging from asymptomatic to severely affected. The classic presentation is failure to thrive, malnutrition, diarrhea, abdominal pain, and distension . Although the development of cardiac morbidity in CD patients has been established in many studies, the exact mechanisms are not exactly known. An increased incidences of dilated cardiomyopathy, ischemic heart disease had been reported in CD patients. The aim of the present study was to assess the effect of CD on cardiac functions to detect any subclinical myocardial affection. This cross-sectional study included 78 children who were divided into two groups: group 1 included 42 patients (24 females and 18 males), with ages ranging from 2 to 18 years; group 2 included 36 age- and sex-matched healthy children (18 males &18 females) with ages ranging from 5 to 18 years. There was no significant sex predominance in celiac patients which was confirmed by previous studies. Our celiac patients had higher systolic blood pressures and lower diastolic blood pressures when compared to the controls, this may be due to hyper dynamic circulation caused by anemia in those patients. It was different from Bayar et al. who found that patients with CD had increased systolic and diastolic blood pressure than the controls; however, his patients were adults with additional risk factors like smoking. In our study, there was no statistically significant difference between patients and controls as regards the FS and EF of the LV (p = 0.915, 0.362 respectively); the same was confirmed by several studies.

Table 3. Pulsed wave Doppler imaging measurements in celiac disease patients and healthy controls

Conventional pulsed Doppler parameters (cm/s)	Cases ($n=42$)	Controls ($n=36$)	*P* value
	Mean ± SD	Mean ± SD	
Tricuspid valve			
E wave velocity	62.45 ± 17.79	82.83 ± 6.39	**< 0.001**
A wave velocity	43.95 ± 16.05	44.08 ± 3.24	0.968
E/A ratio	1.45 ± 0.31	1.89 ± 0.19	**< 0.001**
DT	93.48 ± 25.4	93.17 ± 3.29	0.896
Mitral valve			
E wave velocity	94.66 ± 14.71	97 ± 6	0.324
A wave velocity	55.43 ± 25.44	69.03 ± 3.21	**0.001**
E/A ratio	1.86 ± 0.56	1.41 ± 0.11	**< 0.001**
DT	91.63 ± 27.35	97.22 ± 8.7	0.261

In the current study, we found notably lower TV E/A ratio and higher MV E/A ratio in CD patients than controls ($p = 0.001$). Lower E/A ratio measured by conventional pulsed Doppler indicates diastolic dysfunction of the related ventricle. These results were different from the results of Saylan et al. who found a significantly lower E/A ratio of MV and TV in the patients than the control group and also different from Alkan et al. who found no statistically significant difference between the two groups in MV E, MV A, and MV E/A parameters. This incomparability may be because conventional echocardiography assesses the global systolic and diastolic functions and can miss modest myocardial dysfunction. Tissue Doppler can overcome these limitations and detect preclinical myocardial injury.With TDI of left ventricle, our data revealed systolic dysfunction detected by significantly lower S wave in patients in comparison to controls (8.1 ± 2.3, 10.81 ± 2.61 respectively, $p < 0.001$), and modest LV diastolic dysfunction as evidenced by significantly lower mitral E′/a′, with mean (2.13 ± 0.87) in cases compared to (2.94 ± 0.61) in controls $p < 0.001$. In addition, there were systolic dysfunction of RV as proved by significantly reduced S wave in relation to control (12 ± 2.66, 14.53 ± 2.05, $p < 0.001$) and diastolic dysfunction as detected by increased E/e′ ratio when compared to the control group (6.09 ± 0.8, 4.15 ± 1.33 respectively, $p < 0.001$). These abnormalities were compatible with Fathy et al., who found systolic and diastolic dysfunctions of both ventricles , while incompatible with other studies which reported no evidence of substantial systolic or diastolic dysfunctions measured by these waves .

Table 4 Tissue Doppler imaging measurements in celiac patients and healthy controls

Tissue Doppler parameters (cm/s)	Cases ($n=42$)	Controls ($n=36$)	*P* value
	Mean ± SD	Mean ± SD	
Septal wall			
S wave velocity	7.97 ± 1.44	11.33 ± 1.57	**< 0.001**
E′ wave velocity	13.4 ± 2.72	14.44 ± 1.16	**0.036**
a′ wave velocity	7.22 ± 1.33	7.83 ± 1.13	**0.033**
E′/a′ ratio	2 ± 0.64	1.87 ± 0.25	0.283
Lateral wall (mitral valve)			
S wave velocity	8.1 ± 2.3	10.81 ± 1.62	**< 0.001**
E′ wave velocity	16.38 ± 3.64	15.25 ± 1.25	0.080
a′ wave velocity	8.45 ± 3.45	5.39 ± 1.13	**< 0.001**
E′/a′ ratio	2.13 ± 0.87	2.94 ± 0.61	**< 0.001**
E/e′ ratio	6 ± 1.39	6.41 ± 0.7	0.104
MPI (Tie index)	0.33 ± 0.10	0.35 ± 0.03	**0.04**
Anterior wall (tricuspid valve)			
S wave velocity	12 ± 2.66	14.53 ± 2.05	**< 0.001**
E′ wave velocity	15.62 ± 2.85	13.75 ± 1.48	**< 0.001**
a′ wave velocity	10.42 ± 3.46	8.61 ± 1.1	**0.003**
E′/a′ ratio	1.58 ± 0.55	1.62 ± 0.27	0.676
E/e′ ratio	6.09 ± 0.8	4.15 ± 1.33	**< 0.001**
MPI (Tie index)	0.33 ± 0.08	0.28 ± 0.02	**0.001**

The proposed mechanisms for the development of cardiomyopathy in celiac patients include the nutritional deficiencies which result from chronic malabsorption, the myocardial damage caused by the absorption of variable infectious agents or luminal antigens due to changes in the permeability of the intestine, and the autoimmune process which is the most acceptable theory . Myocardial performance index (MPI) is a sensitive index of systolic and diastolic functions of the ventricles; we found a statistically significant difference in MPI of RV between patients and controls, yet it was within nor mal limits. This relation was not established for the LV. The longer RV MPI in our patients may indicate early dysfunction as proved by the previously described lower waves and ratios. Our results were partially compatible with the results of several studies . they found a significant lengthening of the MPI values for RV and LV in their patients. This difference may be attributed to the variable degree of ongoing inflammation related to the duration and severity of the CD and the strictness of diet control. Patients with extraintestinal manifestations had significantly lower RV E′/a′ ratio than controls (1.5 ± 0.48, 2.16 ± 0.71 respectively, p = 0.009) and lower E′/a′ ratio of the septal wall of LV (1.92 ± 0.52, 2.54 ± 1.11 respectively, p = 0.04) pointing to more cardiac affection in the presence of extraintestinal manifestations in CD patients, possibly due to the increased severity of the inflammatory process, or the addition of more etiological factors to the cardiac dysfunction. Our study was limited by the relatively small number of patients and lack of multiple echo measurements to allow for better comparison.

Table 5. Relation between the presence of extraintestinal manifestations and tissue Doppler results in Celiac patients

Tissue Doppler (TVI) cm/s		Extraintestinal manifestations		Test value	*P* value
		No ($n=5$)	Yes ($n=37$)		
Septal wall					
S	Mean ± SD	7.40 ± 0.89	8.05 ± 1.49	−0.943	0.351
	Range	6–8	5–10		
E′	Mean ± SD	13.67 ± 2.50	13.37 ± 2.78	0.227	0.821
	Range	10.33–17	8.3–18		
a′	Mean ± SD	7.10 ± 0.74	7.24 ± 1.40	−0.210	0.835
	Range	6.3–8	4.3–10		
E′/a′	Mean ± SD	2.54 ± 1.11	1.92 ± 0.52	2.110	**0.041**
Lateral wall					
S	Mean ± SD	7.20 ± 0.45	8.22 ± 2.43	−0.924	0.361
	Range	7–8	5–16		
E′	Mean ± SD	17.00 ± 3.08	16.30 ± 3.74	0.401	0.691
	Range	12–20	9–24		
a′	Mean ± SD	6.00 ± 1.41	8.78 ± 3.52	−1.732	0.091
	Range	4–7	4–21		
E′/a′	Median (IQR)	2(1.7–2.6)	2.2(1.42–2.75)	−0.058 ≠	0.954
	Range	1.7–3	0.14–4		
E/e′	Mean ± SD	5.73 ± 0.63	6.04 ± 1.47	−0.467	0.643
	Range	4.8–6.3	4.29–11		
MPI (Tie index)	Mean ± SD	0.40 ± 0.21	0.32 ± 0.08	1.629	0.111
	Range	0.23–0.75	0.21–0.53		
Anterior wall					
S	Mean ± SD	11.40 ± 1.52	12.08 ± 2.78	−0.533	0.597
	Range	9–13	6–17		
E′	Mean ± SD	16.40 ± 3.36	15.51 ± 2.81	0.647	0.521
	Range	11–20	10–23		
a′	Mean ± SD	7.94 ± 2.28	10.77 ± 3.47	−1.758	0.087
	Range	5–10	5–21		
E′/a′	Mean ± SD	2.16 ± 0.71	1.50 ± 0.48	2.734	**0.009**
	Range	1.65–3.4	0.4–2.4		
E/e′	Mean ± SD	4.16 ± 2.00	4.15 ± 1.25	0.013	0.989
	Range	2.59–7.09	2.4–7.4		
MPI (Tie index)	Mean ± SD	0.29 ± 0.06	0.33 ± 0.08	−1.136	0.263
	Range	0.21–0.36	0.18–0.49		

7.Conclusion and recommendations

Children with CD had early subclinical myocardial dysfunctions especially in the RV (dilated RV, lower E/a ratio, higher E/e′, longer MPI). These early dysfunctions may be exacerbated by the presence of extraintestinal manifestations in our patients. We recommend close collaboration between gastroenterologists and cardiologists by large multicenter studies for screening CD patients for myocardial dysfunctions. Regular tissue Doppler echocardiography for CD patients especially those with extraintestinal manifestations is advised, to detect modest myocardial dysfunctions and lessen CVD-related morbidity and mortality.

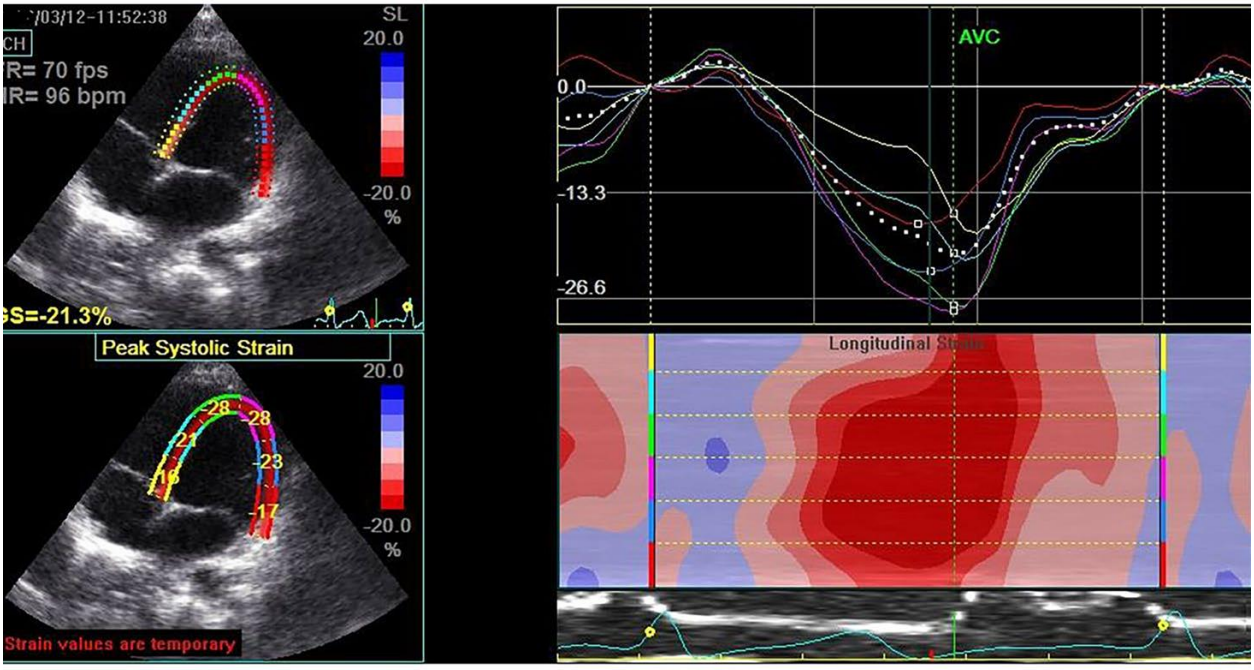

Fig 2. 2D-GLS in a healthy control where LV GLS = -21.3%

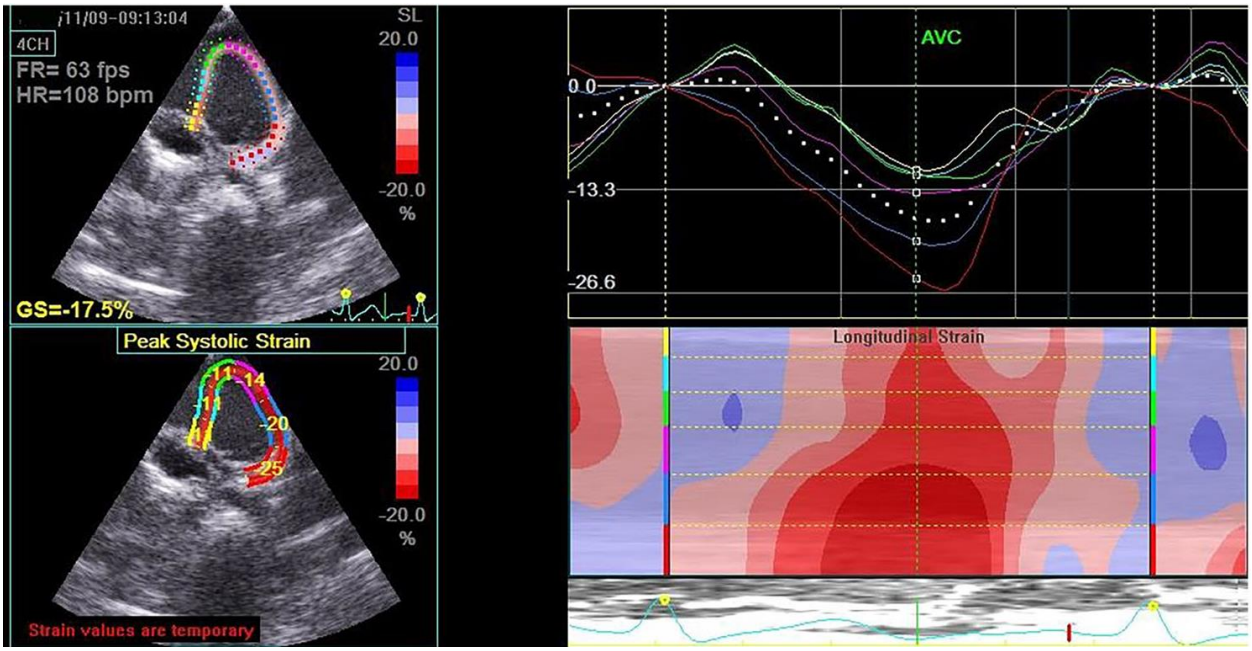

Fig. 3. 2D-GLS in a child with CD where LV GLS = − 17.5%