Celiac disease (CD) is a common autoimmune disorder that occurs in genetically predisposed individuals. It is characterized by an immune response to ingested wheat gluten and related proteins of rye and barley that leads to inflammation, villous atrophy, and crypt hyperplasia in the intestine. The clinical presentations of CD vary widely ranging from asymptomatic forms to severe diarrhea, malabsorption, weight loss, and nutritional deficiencies. CD commonly presents with extraintestinal manifestations as anemia, osteopenia, short stature, or neurological disorders. CD has long been known to be associated with other autoimmune disorders such as diabetes, Hashimoto’s disease, and dermatitis herpetiformis.

CD-associated cardiologic disorders are a growing concern. Some studies have reported an increased prevalence of CD in patients with dilated cardiomyopathy (DCM). Frustaci et al. have reported a relatively high CD prevalence in a large cohort of patients with biopsy-proven myocarditis. Other studies have evaluated the risk of idiopathic DCM in patients with biopsy-verified CD. However, most of these studies cannot confirm a causal relation between CD and DCM. Limited studies have reported the association...
between CD and other cardiac disorders such as atrial fibrillation, pericarditis, ischemic heart disease, and cardiovascular death.

The association between CD and cardiovascular disorders in pediatric population has not been fully investigated. To our knowledge, no previous study has reported an increased prevalence of cardiomyopathy in children with CD, and only few studies have evaluated the subclinical cardiac involvement in children with CD.

Because it is difficult to detect subclinical myocardial changes using conventional techniques that merely evaluate global systolic and diastolic functions, Doppler tissue imaging (DTI) was introduced as a new, noninvasive, and simple echocardiographic method that can assess the ventricular systolic and diastolic functions. DTI is a sensitive indicator for the detection of subclinical myocardial damage and can solve the limitation of the conventional echo techniques that merely evaluate the global systolic and diastolic function. The myocardial performance index or Tei index is a relatively new and powerful index that can be used to assess global systolic and diastolic myocardial function at the same time and has been shown to be significantly correlated with results observed during cardiac catheterization.

The aim of the present work is to assess the subclinical impact of CD on the global myocardial performance in Saudi children with CD using DTI.

**PATIENTS AND METHODS**

**Study population**

A prospective case control study was conducted at the Maternity and Children Hospital, Al Madinah, Saudi Arabia, between February 2015 and August 2015. Twenty consecutive patients with CD were enrolled in the study. The diagnosis of CD in all patients was made based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria. A control group of 20 age and sex-matched healthy children were selected from children presenting to outpatient clinics; the children were thoroughly evaluated to ensure that they do not have any cardiac or gastrointestinal problems.

After explaining the objectives of the study, a written informed consent was obtained from the legal guardians of all enrolled children. The study protocol was approved by the local Ethics Committee prior to the start of study.

None of the included children had preexisting cardiac disorders or was receiving any medication that could affect the cardiac function.

Children included in the study were subjected to thorough history and careful physical examination including detailed anthropometric measurements and cardiac examination. Laboratory investigations were performed for all patients, including complete blood count (CBC), iron profile, calcium, phosphorus, albumin, total IgA, anti-tTG immunoglobulin subclass A (IgA), using enzyme linked immune-sorbent assay (ELISA) and endomysial antibody (EMA) IgA subclass using indirect immunofluorescence assay.

All included children with CD underwent upper gastrointestinal endoscopy, and small intestinal biopsy specimens were obtained for confirming the diagnosis of CD. Biopsies were reviewed by a single pathologist and were reported according to the Modified Marsh Classification of the histologic findings in CD; the pathologist was blinded to clinical and endoscopic data and serologic results.

**Standard echocardiography**

A complete two-dimensional echocardiogram was performed for each participant using the Philips Sonos 7500 or iE33 (Philips Medical Systems, Best, Holland) with a size-appropriate transducer incorporating two-dimensional, color flow, and spectral Doppler. Each study was performed at rest and in supine position without sedation to confirm normal anatomy and function. Transthoracic echocardiography was performed by an experienced pediatric cardiologist. Echocardiography was performed while the patients were at rest and in the supine position. Images were recorded on videotapes. Conventional echocardiographic measurements were obtained according to the guidelines of the American Society of echocardiography. At least three consecutive beats in sinus rhythm were recorded, and average values were obtained to represent the cardiac function.

**Pulsed-wave Doppler tissue imaging studies**

This method is capable of providing measurements of ventricular wall motion velocity by positioning the sample volume at mitral and tricuspid valve annuli. In the apical four-chamber view, the pulsed Doppler sample volume was placed at the lateral margin of the mitral annulus and lateral margin of the tricuspid annulus. Care was taken to obtain an ultrasound beam parallel to the direction of the annular motion.

The detailed DTI measurements are shown in Figure 1. The interval (a) between the end of the late diastolic annular velocity and the onset of the early diastolic annular velocity were equal to the sum of the isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET). The ET (b) was measured as the duration of the systolic annular velocity (Sm). The sum of the ICT and IRT was obtained by subtracting (b) from (a). The IRT was measured from the pulsed-wave Doppler tissue recordings as...
the time interval from the end of the systolic annular velocity to the onset of the early diastolic annular velocity, and the ICT was obtained by subtracting the IRT from \((a-b)\). Then, the left ventricular (LV) Tei and right ventricular (RV) Tei indexes were calculated as \((a-b)/b\). The ICT and ET are affected by systolic dysfunction whereas IRT is affected by diastolic dysfunction. Consequently, Tei index is regarded as a valuable index for assessing global systolic and diastolic myocardial function at the same time.

All parameters were measured during end expiration and three consecutive images were recorded; the mean values of these measurements were used for statistical analysis. All recordings were made using a sweep speed of 100 mm/s, with a simultaneous electrocardiogram (lead II) at these locations and stored on videotape for subsequent analysis.

**Statistical analysis**

Data were statistically analyzed with the use of the Statistical Package for Social sciences software (SPSS version 16.0 for windows, Chicago, IL). The quantitative data were presented as mean ± standard deviation (SD). Variables were compared between groups by using the unpaired t-test. \(P\) value of <0.05 was considered to be significant. Pearson’s correlation coefficient was used to assess the correlation between various parameters. To assess inter observer variability, DTI data from video recordings of 10 randomly selected patients were analyzed twice by the same observer within a period of time between the two observations of approximately 2 weeks. Intra observer variability is expressed as the mean difference ± SD between the two observations.

**RESULTS**

Twenty children (8 males and 12 females; mean age 8.2 ± 2.7 years) with CD were included in this study; 15 patients were recently diagnosed cases who were enrolled in the study prior to initiation of a gluten free diet (GFD) and 7 patients were old cases who were noncompliant on the GFD and still symptomatic at the time of enrollment in the study (mean follow-up time was 32.2 ± 17.1 months). All patients had positive EMA at the time of enrollment. Twenty healthy age and sex-matched children were taken as the control group. Clinicoepidemiologic data and laboratory investigations of the studied children are shown in Table 1.

**Standard echocardiography results**

Conventional M-Mode echocardiography indices of the patient and control groups are shown in Table 2. No

**Table 1: Clinicoepidemiologic data and laboratory investigations of the studied children**

| Parameter                              | Patients (n=20) | Control (n=20) | \(P\) |
|----------------------------------------|----------------|----------------|------|
| Clinicoepidemiologic data              |                |                |      |
| Age (years)                            | 8.2±2.7        | 8.2±2.6        | 0.96 |
| Sex (male/female)                      | (8/12, 40-60%) | (7/13, 35-65%) | 0.74 |
| Weight (Kg)                            | 22.6±6.6       | 26.2±7.2       | 0.10 |
| Height (cm)                            | 118.7±16.6     | 127.4±15.4     | 0.96 |
| Mean pulse rate (beats/min)            | 92±13.3        | 93.5±14        | 0.73 |
| Mean diastolic blood pressure (mmHg)   | 60.5±6.7       | 60.3±6         | 0.9  |
| Laboratory investigations              |                |                |      |
| Hemoglobin (gm/dL)                     | 12.3±0.9       | 12.4±0.8       | 0.64 |
| Platelet count (cell/mm\(^3\))         | 354.2±101.9    | 359.4±96.9     | 0.87 |
| WBC count (cell/mm\(^3\))              | 8100±2900      | 7500±2200      | 0.79 |
| AST (IU/L)                             | 30.2±8.5       | 28.9±5.7       | 0.58 |
| ALT in (IU/L)                          | 27.7±6.2       | 27.8±6.2       | 0.96 |
| Serum albumin (gm/dL)                  | 40.7±3         | 38.3±3.8       | 0.33 |
| Alkaline phosphatase (U/L)             | 317.2±99.4     | 310.2±86.4     | 0.92 |

**Table 2: Conventional echocardiographic measurements in Celiac disease patients and healthy controls**

| Parameter                              | Patients (n=20) | Controls (n=20) | \(P\) |
|----------------------------------------|----------------|----------------|------|
| LV and RV structure, volumes, systolic functions (M-Mode): |                |                |      |
| RVDD (cm)                              | 1.33±0.43      | 1.33±0.43      | 0.63 |
| LVIDs (cm)                             | 2.93±0.37      | 2.93±0.37      | 0.28 |
| LVIDd (cm)                             | 4.57±0.56      | 4.57±0.56      | 0.29 |
| LA Volume (mL)                         | 45.38±8.3      | 42.05±7.8      | 0.69 |
| AorR diameter (cm)                     | 2.39±0.28      | 2.39±0.28      | 0.38 |
| LV FS %                                | 35.7±3.45      | 35.7±3.45      | 0.74 |
| ETC (ms)                               | 348±27.9       | 339±15.7       | 0.168|
| LV and RV Diastolic functions:         |                |                |      |
| Mitral inflow                          |                |                |      |
| E wave (cm/s)                          | 7.75±1.38      | 7.91±1.27      | 0.52 |
| A wave (cm/s)                          | 4.76±1.0       | 4.92±1.0       | 0.39 |
| E/A ratio                              | 1.68±0.41      | 1.67±0.45      | 0.89 |
| Tricuspid inflow                       |                |                |      |
| E wave (cm/s)                          | 6.25±0.26      | 6.23±0.27      | 0.70 |
| A wave (cm/s)                          | 3.34±0.12      | 3.34±0.13      | 0.85 |
| E/A ratio                              | 1.87±0.09      | 1.86±0.09      | 0.63 |
statistically significant difference existed between CD patients and the control children with respect to the means (±SD) RV diastolic diameter (RVDd) ($P = 0.63$), LV internal dimensions in systole and diastole (LVIDs and LVIDd) ($P = 0.28$ and 0.29, respectively), left atrium volume ($P = 0.69$), aortic root (AoR) diameter ($P = 0.38$), LV fractional shortening (LV FS) ($P = 0.74$), and corrected ejection time (Etc) ($P = 0.16$). In addition, the two groups showed no significant difference regarding mitral inflow velocities, E/A ratio ($P = 0.89$), the tricuspid inflow velocities, and E/A ratio ($P = 0.63$).

**Pulsedwave Doppler tissue imaging results**

DTI measurements and LV and RV Tei indexes of both groups are shown in Table 3. CD patients, in comparison to the control group, were found to have significantly lower mitral systolic (Sm) wave velocity, mitral annular Em wave velocity ($P < 0.001$), Em/Am ratio ($P < 0.001$) values, and higher mean E/Em ratio (0.0006). They had significantly prolonged ICT and IRT values and shortened ET, and consequently higher LV Tei index values ($P < 0.0005$). Mitral annular Am wave velocity did not differ significantly between the two groups.

Tricuspid annular Sm wave velocity, Em wave velocity, and the Em/Am ratio were reduced in patients with CD compared to controls. In addition, they had increased E/Em ratio ($P < 0.001$), prolonged ICT and IRT, shortened ET, and higher RV Tei index value ($P < 0.0001$). Tricuspid annular Am wave velocity showed no significant difference in CD patients compared to controls.

As shown in Figure 2, the Modified Marsh Classification of the histologic findings in CD patients were significantly positively correlated with the RV Tei index ($r = 0.7753$, $P < 0.0001$). Although the LV Tei index seems to be more affected in patients with more severe histologic findings according to Modified Marsh Classification, this relation did not reach statistical significance ($r = 0.2479$, $P = 0.292$). On the other hand, FS was not correlated with the Modified Marsh Classification ($r = -0.11$, $P = 0.641$).

**DISCUSSION**

CD commonly presents with extra-intestinal manifestations, however, cardiac involvement in children with CD is still not fully evaluated. In the present study, we evaluated myocardial functions in Saudi children with CD using conventional echocardiographic study and DTI. We did not detect any statistically significant differences between CD patients and healthy controls regarding the conventional echocardiography indices. Similar findings were reported by Polat *et al.*\[22\] who reported no difference between CD patients and healthy controls regarding the absolute values of the dimensions of the cardiac chambers as well as the parameters that are commonly used to assess the LV function as left ventricular ejection and shortening fractions. Saylan *et al.*\[23\] reported no significant difference between CD children and healthy controls regarding the ejection fraction and FS parameters, however, the interventricular septal systolic dimension (IVSD) and LV end diastolic diameter (LVEDD) parameters were significantly different between EMA (+) and EMA (−) groups as well as the control group.

| Table 3: Dopplertissue imaging measurements in Celiac disease patients and healthy controls |
|---------------------------------|-----------------|-----------------|---|
| Parameter                        | Patients (n=20) | Controls (n=20) | $P$ |
|---------------------------------|-----------------|-----------------|---|
| **Mitrail annulus**             |                 |                 |   |
| Mitral peak systolic (Sm) velocity (cm/s) | 7.04±1.22 | 8.1±1.12 | <0.001* |
| Mitral early diastolic (Em) velocity (cm/s) | 12.4±2.09 | 15.29±1.75 | <0.001* |
| Mitral late diastolic (Am) velocity (cm/s) | 6.09±1.56 | 6.27±0.84 | 0.28 |
| Mitral Em/Am ratio               | 2.11±0.53       | 2.3±0.19       | <0.001* |
| Mitral ICT (ms)                  | 68.9±19.7       | 50.49±5.5      | <0.001* |
| Mitral IRT (ms)                  | 85.77±23.2      | 52.9±6.11      | <0.001* |
| Mitral E/Em ratio                | 0.66±0.11       | 0.52±0.23      | 0.0006* |
| Mitral ET (ms)                   | 242.3±26.9      | 327.3±9.06     | <0.001* |
| Left ventricular Tei index       | 0.47±0.05       | 0.31±0.18      | <0.0005* |
| **Tricuspid annulus**            |                 |                 |   |
| Tricuspid peak systolic (Sm) velocity (cm/s) | 9.32±2.4 | 11.98±0.78 | <0.001* |
| Tricuspid early diastolic (Em) velocity (cm/s) | 11.67±3.01 | 16.15±1.09 | <0.001* |
| Tricuspid late diastolic (Am) velocity (cm/s) | 7.82±1.9 | 7.74±0.9 | 0.73 |
| Tricuspid Em/Am ratio            | 1.57±0.40       | 2.11±0.1       | <0.001* |
| Tricuspid ICT (ms)               | 66.15±21.4      | 41.97±7.23     | <0.001* |
| Tricuspid IRT (ms)               | 81.02±15.4      | 46.09±5.09     | <0.001* |
| Tricuspid E/Em ratio             | 0.58±0.18       | 0.36±0.05      | <0.001* |
| Right ventricular Tei index      | 0.51±0.04       | 0.32±0.05      | <0.0001* |

* $P$ value = 0.0068
Lionetti et al.,[24] in a study among 40 children with CD, using two-dimensional and M-mode echocardiography detected mild cardiac affection in 9 out of 40 patients in the form of mitral valve regurgitation (5 patients), aortic valve regurgitation (2 patients), pulmonary and tricuspid valve regurgitation (1 patient), and low ejection fraction (1 patient). Furthermore, they reported improvement of these cardiac alterations after 12 months of a strict GFD.

Although the association of CD with DCM has been described in many studies on adult population,[25] published data in pediatric populations are few. In a study conducted by Zahmatkeshan et al. to evaluate the prevalence of CD in patients with DCM, 1 out of 41 (2.5%) DCM cases were found to have positive tTG antibody level and negative intestinal biopsy.[26] There are some published case reports of CD associated with myocarditis or cardiomyopathy.[27] In our study, none of the CD patients had any degree of DCM.

DTI is now considered to be a sensitive indicator that can detect subclinical myocardial damage and can solve the limitation of conventional echo techniques that merely evaluate the global systolic and diastolic function.[16,17] In our study, CD children had LV systolic dysfunction in the form of significant decrease in mitral peak systolic (Sm) velocity. In addition, they had LV diastolic dysfunction in the form of decreased mitral annular Em wave velocity, Em/Am ratio, as well as significantly higher E/Em ratio. Similarly, there was RV systolic dysfunction in the form of decrease in tricuspid peak systolic (Sm) velocity, and RV diastolic dysfunction (decreased tricuspid annular Em wave velocity, Em/Am ratio, and higher E/Em ratio). In addition, we reported significant prolongation in the IRT and ICT at the mitral annulus and at the tricuspid annulus in CD patients compared to healthy children. Potal et al.,[22] in their study, reported decreased overall Sm velocity of the mitral and tricuspid annuli in CD patients as compared to healthy controls. Furthermore, Saylan et al.[23] reported a significant difference in DTI parameters including mitral valve early diastolic (Em) velocity, mitral valve late diastolic (Am) velocity, mitral Em/Am ratio, tricuspid valve early diastolic (Em) velocity, and LV myocardial performance index between CD patients and the control groups.

Figure 2: Correlation between Doppler tissue imaging and endoscopic Marsh grading using Pearson’s correlation coefficient
We suggest that variations in the severity and nature of cardiac involvement in patients with CD may be, in part, related to variation in the disease severity and duration of illness or it may be related to certain genetic susceptibility.

This study is the first to report the Tei index of both ventricles using DTI in children with CD. We detected a statistically significant increase in both the LV and RV DTI-derived Tei index in children with CD. The use of TDI to calculate Tei Index is more accurate than using conventional echocardiography because the time intervals between the end and onset of diastolic annular velocities are easier to measure. Moreover, it is more accurate to calculate Tei index within a single cardiac cycle away from heart rate fluctuation.[32,29]

Although the development of cardiac affection in patients with CD has been established in many studies, the exact mechanisms underlying such affection are not exactly known. CD commonly leads to chronic malabsorption that may lead to cardiomyopathy secondary to nutritional deficiencies.[30] In addition, CD causes abnormalities of intestinal permeability that may lead to increased systemic absorption of various luminal antigens or infectious agents that may cause myocardial damage.[31] The most acceptable explanation for the link between CD and cardiac affection is that both conditions might be mediated through autoimmune mechanisms.[32] Previous studies in autoimmune disorders such as systemic lupus erythematosus and autoimmune hepatitis have shown that occurrence of systolic and diastolic impairments in these conditions may be related to some nonspecific myocardial lesions (focal or generalized myocarditis), which were found in the autopsy of these autoimmune disease specimens.[33,34] Similar mechanism could be suggested in patients with CD.

Claudins are small transmembrane proteins that form a major structural component of tight junctions in epithelia and endothelia and can be found in all the organs of the body.[35] At present, claudins have been found to play a role in the pathogenesis of diseases of the intestinal tract including CD.[36] Further, they have been related to the development of cardiomyopathy.[37] Several studies have reported alteration in the expression of claudinsin CD with upregulation of channel-forming claudin-2 and 15 and downregulation of tightening claudin-3, 5, 7 in active CD.[38,39] Such alterations contribute to the severe barrier impairment in CD. On the other hand, alterations of a tight junction protein have been reported in human cardiomyopathy samples, and it has been suggested that reduction in claudin-5 may participate in the pathway to end-stage heart failure.[40]

**Study limitations**

Lack of data concerning the progression of the cardiac affection patient group and response to GFD are the most important limitations of our study. Small number of patients enrolled in this study is another limitation; hence, larger multicenter studies involving more patients are needed to confirm our findings of subclinical cardiac affection in CD patients. In addition, evaluation of vitamins and nutrient deficiencies in children with CD and cardiac abnormalities needs to be considered in future studies.

**CONCLUSION**

Subclinical myocardial dysfunction of both ventricles occurs in children with CD. The DTI method appears to be more sensitive than the conventional two-dimensional echocardiography in the early detection of myocardial dysfunction in children with CD.

**Financial support and sponsorship**

Deanship of Scientific Research (DSR), Taibah University, Madinah, Saudi Arabia, grant no. 6137/1435.

**Conflicts of interest**

There are no conflicts of interest.

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