Echocardiographic and biochemical profile in children with celiac disease

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ABSTRACT

Background: A number of heart diseases such as autoimmune myocarditis, cardiomyopathy, and ischemic heart disease are recently being reported among celiac patients. Studies have also demonstrated subclinical cardiac dysfunction and clustering of many traditional cardiovascular risk factors in children with celiac disease. **Objective:** The present study was conducted for echocardiographic and biochemical assessment of children with celiac disease. **Materials and Methods:** A cross-sectional observational study was conducted among 36 children (aged 1–16 years) who were newly diagnosed with celiac disease and age- and sex-matched controls. Venous blood samples were assessed for serum C-reactive protein (CRP), folic acid, Vitamin $B_{12,}$ and homocysteine levels, and fasting lipid profile including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) levels using appropriate methods. Echocardiographic parameters were measured by M-mode ultrasonography measuring left atrial dimension (LAD), left ventricular end-diastolic dimension (LVEDD), right ventricular diastolic diameter (RVDD), interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), aortic root dimension (ARD), and ejection fraction (EF). **Results:** Among the echocardiographic parameters, EF was significantly lower while other parameters such as LAD, LVEDD, RVDD, IVSd, LVPWd, and ARD showed no significant increase among the cases. Significantly lower levels of TC, HDL-C, and LDL-C with normal TG, CRP, Vitamin B_{12}, and folic acid levels with significantly increased serum homocysteine levels were noted among cases. **Conclusion:** A significant difference in EF and the presence of biochemical risk factors for cardiovascular diseases warrants further detailed evaluation and follow-up with regular monitoring of cardiac functions.

Key words: *Cardiomyopathy, Cardiovascular risk factors, Celiac disease, Echocardiography, Homocysteine, Lipid profile*

Celiac disease is a chronic small bowel enteropathy with an underlying autoimmune mechanism precipitated by exposure to dietary gluten in genetically predisposed people. It is the most common cause of chronic diarrhea in children in many parts of the world and accounts for 26% and 56% of chronic diarrhea among adults in Western and Northern India, respectively. Recently, heart diseases due to idiopathic and immune pathogenesis, including autoimmune myocarditis, cardiomyopathy, impaired aortic function, ischemic heart disease, arrhythmias, cerebrovascular diseases, syncope, and sudden death are being reported among the celiac patients [1-3]. These may be attributed to the chronic systemic inflammation, early atherosclerosis, unfavorable biochemical profile, and the autoimmune process.

Clustering of cardiovascular risk factors is evident in childhood and persists into young adulthood, especially in patients with numerous associated comorbidities such as celiac disease. C-reactive protein (CRP) is an important marker of inflammation and has a strong linear relationship with the incidence of cardiovascular events. While low-density lipoprotein cholesterol (LDL-C) has a critical role in atherogenesis, high-density lipoprotein cholesterol (HDL-C) is regarded as a potent anti-atherogenic mediator with anti-inflammatory, anti-oxidative, and anti-thrombotic properties. Celiac patients have most commonly shown an association with hypocholesterolemia with low levels of total cholesterol (TC), LDL-C, and HDL-C.

Celiac patients are more prone to develop deficiencies Vitamin B_1, B_2, B_6, folate, and Vitamin B_{12} even after adhering to a strict gluten-free diet (GFD) for years with biopsy-proven remission. These vitamins also play an important role in homocysteine metabolism. Hyperhomocysteinemia in untreated patients can be linked to cardiovascular disease. Studies have described the coexistence of myocarditis, dilated cardiomyopathy, and resultant increased incidence of heart failure among patients with celiac disease [3-7]. There are a few Indian studies on echocardiographic abnormalities and metabolic derangements in children with celiac disease [8,9]. Hence, the present study was conducted to evaluate echocardiographic and biochemical profiles in children with the celiac disease aged 1–16 years in comparison to age- and sex-matched controls.

MATERIALS AND METHODS

This cross-sectional observational study was conducted from November 2015 to March 2017. With the standard deviation (SD) (7.93, 0.66) for left ventricular end-diastolic diameter (LVEDD) (mm), power of 90% and an alpha level of 0.05, a total of 72 children were required to complete the study [10]. A total of 36 children (aged 1–16 years) newly diagnosed with celiac disease and 36 age- and sex-matched controls from children attending the hospital outpatient department were enrolled. Ethical clearance was obtained from the hospital committee and informed written consent was taken from all the parents/guardians before the enrolment.

Celiac disease was defined based on the World Gastroenterology Organization – Guidelines for Celiac Disease 2012 [11]. Children already diagnosed and on treatment with GFD before the start of the study were not included in the study as it can modify the disease process and alter the results. Children diagnosed with any other associated known chronic infections/ inflammatory diseases or syndromes were excluded from the study. Venous blood from a peripheral vein was drawn after overnight fasting and samples were collected for estimation of CRP (laser nephelometry), serum fasting lipid profile including TC, triglycerides (TG) (cholesterol oxidase and colorimetric methods), HDL-C levels (direct non-immunological assay), LDL-C (Friedwald, 1972; formula), serum folic acid, and Vitamin B_{12} (chemiluminescence method).

Echocardiographic parameters were measured by M-mode ultrasonography (Philips HD 11 XE) by single experienced cardiologist blinded to clinical and laboratory data. Variables such as left atrial dimension (LAD), LVEDD, right ventricular diastolic diameter (RVDD), interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), aortic root dimension (ARD), and ejection fraction (EF) were measured and assessed accordingly [12].

Statistical analysis was performed by SPSS version 17.0. Continuous variables were presented as mean±SD, and categorical variables were presented as absolute numbers and percentages. Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann–Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the Chi-square test or Fisher's exact test. Spearman correlation was performed to determine the relationship between different variables. For all statistical tests, $p<0.05$ was statistically significant.

RESULTS

In cases and controls, age distribution was comparable with the mean age of 7.72±3.26 years and 7.56±3.18 years, respectively, with male:female ratio of 5:4. The mean age at onset of symptoms among cases was 5.86±3.09 years and the mean duration of illness before diagnosis was 22.47±18.00 months. Echocardiographic and biochemical parameters recorded in the cases and controls given in Table 1.

Among cases and controls, 50.0% and 2.8% had wasting ($p<0.001$), 61.1% and 5.6% had stunting ($p<0.001$), and 8.3% and 22.2% were overweight, respectively. Furthermore, among the cases, 16.7% were underweight, and among controls, 11.1% were obese ($p=0.006$). Although it was statistically insignificant, the study population had a greater proportion of the children with higher TC to HDL-C ratio ($p=0.465$) and higher TG levels ($p=0.155$) but demonstrated lower levels of LDL-C ($p=0.076$) as compared to the controls.

Mean of echocardiographic parameters such as LAD, LVEDD, RVDD, IVSd, and LVPWd did not differ between the cases and controls, while ARD was significantly higher among the controls. EF was significantly lower among the cases with a mean of 63.3±3.59% versus 66.42±3.32% ($p=0.001$) in cases and controls, respectively. There was no significant correlation of all the cardiac echo parameters studied with homocysteine, CRP, or Vitamin B_{12} levels. A negative correlation coefficient was observed between LAD and LVEDD with respect to TG ($p<0.05$). However, no correlation was seen with respect to other parameters. No significant correlation was found between cardiac echo parameters and serum TC, HDL-C, LDL-C, and TC/ HDL-C.

DISCUSSION

Although celiac disease is typically defined as a chronic gastrointestinal disease, it also affects various organ systems directly or indirectly. Many studies have found an increase in the levels of CRP as a marker of inflammation in celiac disease, including those by Pitocco *et al*. [4] and De Marchi *et al*. [13] But like a previous study by Demir *et al*., [5] our study did not demonstrate any significant rise in CRP levels among cases though the levels were higher than in controls and higher than normal in 10 of 36 cases.

Table 1: Echocardiographic and biochemical parameters in the cases and controls

Parameter (mean±SD)	Cases	Controls	p-value
Echocardiographic parameters (mm)			
LAD	21.61±3.57	23.17±5.02	0.304
LVEDD	31.33±4.25	33.36±6.72	0.180
RVDD	22.47±4.58	22.17±3.4	0.892
IVSd	6.22±1.53	6.14±1.27	0.689
LVPWd	6.22±1.73	6.00±1.15	0.869
Laboratory parameters			
TC (mg/dl)	129.97±39.29	150.47±28.1	0.005
HDL-C (mg/dl)	38.25±12.88	46.69±11.6	0.002
LDL-C (mg/dl)	72.88±31.26	89.19±31.869	0.040
TG (mg/dl)	100±47.04	104.56±37.864	0.417
TC/HDL-C	3.59±1.01	3.32±0.87	0.279
CRP (mg/dl)	1.3±2.21	1.028±2.4652	0.305
Homocysteine (μmol/L)	14.1±10.35	6.78±2.41	<0.001
Vitamin B_{12} (pg/dl)	327.11±176.16	381.19±153.51	0.114
Folic acid (ng/dl)	5.96±4.17	8.039±5.4696	0.051

In the present study, TC, HDL-C, and LDL-C levels were significantly decreased. As shown in Table 2 TG was lower and the ratio of TC to HDL-C was higher among the cases but failed to show any statistically significant difference. Thus, the changes observed in the lipid profile of the celiac patients might be detrimental despite a decrease in absolute levels due to altered proportions of HDL and LDL-C. Pitocco *et al*. [4] in their study demonstrated lower values of TC and HDL-C and higher values of TG and LDL-C as compared to the control population, although these results were not statistically significant.

De Marchi *et al*. [13] observed significantly lower levels of TC, LDL, HDL-C, and TG which was in accordance with our study. These two studies included young adult patients; however, the study by Demir *et al*. [5] included children from 6 to 18 years but with non-significant results.

The mean homocysteine level in cases was significantly more that of the controls. Although the Vitamin B_{12} and folic acid levels were also lower among the cases, the difference was not statistically significant. There were 58.3% of the cases who had increased homocysteine levels, while 11.1% and 8.3% had Vitamin B and folic acid deficiency. De Marchi *et al*. [13] and Hallert *et al*. [6] also found similar results with normal Vitamin B_{12} and folic acid levels among the celiac. While Hallert *et al*. [6] and Valente *et al*. [7] found near-normal levels, De Marchi *et al*. [13] and Zanini *et al*. [14] recorded increased homocysteine levels. Many studies, including one by Dickey *et al*. [15], demonstrated decreased serum, red cell folate levels, and Vitamin B_{12} levels, which were unlike our study.

Our cases did not demonstrate a significant increase in any of the echocardiographic parameters. A significantly decreased EF with a mean of 63.3±3.59 % versus 66.42±3.32% with p=0.001 was recorded. A total of 88.9% of the cases as well as controls showed increased RVDD with no statistical difference. There were 41.7% of our cases who demonstrated below normal EF as opposed to only 11.1% of the controls, although none of them were clinically symptomatic. Lionetti *et al*. [16] demonstrated cardiac involvement with impairment of EF in 21% of the patients enrolled. In 2016, Fathy *et al*. [17] also studied RVDd, LVEDD, LAD, ARD, and EF and did not find any significant difference.

Table 2: The percentage distribution of the changes in biochemical parameters

Parameter	Cases (%)	Control (%)	p-value
CRP (increased)	27.8		0.257
Total cholesterol			Non-significant
Lower	30.6	13.9	
Normal	61.1	80.6	
Higher	8.3	5.6	
HDL-C (lower)	44.4	5.6	0.001
Serum homocysteine (>11.3 µmol/L)	58.3	13.9	0.001
Vitamin B_{12} (decrease)	11		Non-significant
Folic acid (decrease)	8.3		0.107

A significant positive correlation between LVEDD, RVDD, ARD, and age of the patient, LVEDD, RVDD, IVSd, ARD, and age at onset of the symptoms, and a significant negative correlation between IVSd and duration of illness were observed. Furthermore, a significant positive correlation between IVSd and serum folic acid levels and a significant negative correlation between LAD and serum folic acid levels, LAD and TG levels, and LVEDD and TG levels were noted in cases of celiac disease. Since none of the previous studies have looked for such correlations, it needs a more detailed evaluation for further justification. None of the studies evaluating ECHO parameters among the celiac patients evaluate the correlation of cardiac dysfunction with other clinical and biochemical parameters.

There were a few limitations. Our study demonstrated a significant difference in EF and deranged biochemical profile but failed to show any clinically significant result. Furthermore, our echocardiographic evaluation was restricted to structural parameters. Dynamic parameters evaluating aortic functions, valvular function, and rhythm abnormalities could have given more insight into the topic.

CONCLUSION

Further studies are needed to determine the frequency and mode for screening children with celiac disease for early markers of cardiovascular involvement.

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