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Original Research

Cardiac Co-Morbidities in Celiac disease in Children and Adolescents

Nihal[1], Manmeet Kaur[2], Rajiv Arora[3]

[1]Junior Resident, Department of Pediatrics , GMC Amritsar
[2] Professor Head & Department of Pediatrics , GMC Amritsar
[3] Professor Head & Department of Cardiology, GMC Amritsar

Correspondence Author
Manmeet Kaur Sodhi
Professor Head & Department of Pediatrics, GMC Amritsar

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Abstract:
Background: Children and adolescents with celiac disease presents with intestinal as well as extra intestinal manifestations. Cardiovascular system has also been found to be involved in the disease process due to the immune mediated mechanisms. Like any other, if not identified and intervened early, cardiac involvement can also progress to advanced stages and can therefore worsen the quality of life and prognosis of celiac disease patients. This calls out for the need of monitoring and following up this population for such complications.
Objectives: Tostudytheassociationofclinicalandsubclinicalcardiaccomorbiditiesin children and adolescents (1-18 years) diagnosed with celiac disease.
Method: This cross-sectional study was conducted at Government Medical College, Amritsar, in collaboration between the Department of Pediatrics and the Department of Cardiology. 30 subjects of celiac disease diagnosed either with serology or histopathology or both were included in the study. They underwent chest Xray, electrocardiography and echocardiography.
Results: Out of the 30 subjects studied, 10% had CT ratio >0.60 indicating cardiomegaly. Electrocardiography revealed variations in 43.34% with sinus tachycardia the most common among them. Echocardiography revealed myocarditis in 30.00%, pericardial effusion in 23.33% and variable degrees of systolic dysfunction in terms of reduced ejection fraction in 76.66%.
Conclusions: This study reveals presence of significant cardiovascular parameter abnormalities indicating that celiac disease has a significant impact on cardiac health. This highlights the importance of early diagnosis and intervention to manage cardiac comorbidities in this group.
Key words: celiac disease, cardiac comorbidities

Introduction:

Celiac disease is an immune mediated disorder caused by gluten &prolamines in genetically susceptible individuals with HLA DQ2/DQ8 haplotypes[1].There is disequilibrium of intraepithelial lymphocyte(IEL) while IL-15 causes expression of natural killer receptors CD94 and NKG2D enhancing cytotoxicity, cell apoptosis, and villous atrophy. The persistent inflammation produces autoantibodies, anti-tTG (anti tissue transglutaminase) and anti-EMA (anti endomyseal antibody) which results in additional tissue damage. There is injury of small intestine mucosa impairing the ability to absorb essential nutrients, resulting in malabsorption[2].Celiac disease prevalence is higher among the immediate family members of individuals with the condition (10–15%) and in other high-risk groups, particularly those with Down syndrome, type 1 diabetes, or IgA deficiency[3]. Preliminary testing for celiac disease is frequently advised for these groups[4].
Clinical presentation can be intestinal or extra-intestinal. Intestinal is common in ones diagnosed within 2 years of age[5]. Most predominant extraintestinal manifestation is iron deficiency anemia which is usually refractory to oral iron therapy due to impaired gastrointestinal absorption.The subclinical form includes patients who have symptoms or signs that fall below the threshold for clinical diagnosis and are often only recognized after experiencing advantages of a gluten-free diet(GFD)[6].Silent celiac diseaseis mainly detected in asymptomatic immediate relatives of people with celiac disease and in patients with conditions associated with celiac disease[7,8].
For diagnosis, measure blood total IgA levels and anti-tTG2 IgA Ab. If anti-tTG2 Ab levels are <10x times higher than normal, upper endoscopy & biopsy is done. If anti-tTG2 Ab levels are >10x of upper normal cutoff, anti-endomysial Ab(EMA) is done. If EMA test are also positive, it verifies celiac disease.Patients having antibodies definite to celiac disease without small intestinal damage are considered to have potential celiac disease[9].The seronegative form has no detectable serological markers despite the presence of malabsorption and

mucosal atrophy of intestine[10].
Recently, cardiac involvement in the form of cardiomyopathy, pericarditis, ischemic heart disease, atrial fibrillation etc has been reported attributing to myocardial damage due to increased absorption of luminal Ag & infectious agents. Disrupted intestinal architecture also allow endotoxins to reach the heart. There is also malabsorption of essential nutrients like vitamin B12 and folic acid, which are crucial for cardiovascular health[11].
Gluten free diet(GFD)is crucial for managing symptoms and preventing complications. It demands significant dietary adjustments and constant vigilance to avoid gluten contamination.The term "non-responsive celiac disease" refers to gastrointestinal symptoms that persist despite not taking gluten in diet for over 12 months[12].a patient shows suboptimal response to gluten withdrawal, careful assessment is needed to ensure adherence to the advised diet. In such cases, a histopathology of duodenumis advisable[13].Unlike adults, refractoryceliac diseaseare rare in children, only a few cases notified[14].
Celiac disease affects the quality of life with children facing social challenges related to attending parties, school events, and dining out, necessitating awareness among caregivers, teachers, and peers.

Objectives: To study the association of clinical and subclinical cardiac comorbidities in children and adolescents (1-18 years) diagnosed with celiac disease.

Method: This cross-sectional study was conducted in Government Medical College, Amritsar in collaboration between the Department of Pediatrics and the Department of Cardiology from Jan-2023 to Dec-2023.

Inclusion and exclusion criteria: 30 subjects diagnosed of celiac disease either with serology (total IgA, anti-tTG, anti-EMA) or histopathology (as mentioned in the diagnosis of celiac disease above) were included in the study while excluding the ones with any endocrine abnormality which could have affected the cardiovascular status.
The required biogeographical details was procured using a detailed proforma. The subjects who met the inclusion criteria and gave informed consent underwent a panel of investigations including Chest Xray, Electrocardiography & Echocardiography.

Ethical issues: The study was approved by the Institutional Ethics Committee of Government Medical College, Amritsar, India (Ref. No. 10794/D-26/2021) on 03.04.2023. Written informed consent was obtained from guardians/parents of the participating children.

Statistical analysis: Data were compiled, computed and analysed using latest version of SPSS. Parametric data were presented as mean ± standard deviations and categorical data were presented as numbers and percentages. Difference in proportion was analysed using Chi square test and difference in means using student t-test or ANOVA as appropriate. Non-parametric data were expressed as median (interquartile range) and analysed using Mann Whitney U test. Single linear regression model was used were applicable. $p<0.05$ was considered statistically significant.

Results:
Table 1 shows the age wise distribution of the study population. The highest proportion of participants fell within the 3 to 7 years age group (36.66%).

Table 1: Age wise distribution of the study population (N=30)

Age group	Number	%
≤ 3 years	6	20.00
3 to 7 years	11	36.66
7 to 10 years	5	16.67
≥ 10 years	8	26.67

The gender-wise distribution of the study population showed a nearly equal representation with females comprising 53.33%.

Table 2: General examination findings present (N=30)

Clinical finding	**Number**	**%**
Pallor	12	40.00
Icterus	0	0.00
Clubbing	2	6.67
Cyanosis	0	0.00
Lymphadenopathy	4	13.33
Edema	5	16.67

Figure 1 shows the distribution of vital parameters among the study population and Figure 2 shows the systemic examination findings.

Fig 1: Distribution of cardiorespiratory parameters in the study population (N=30)

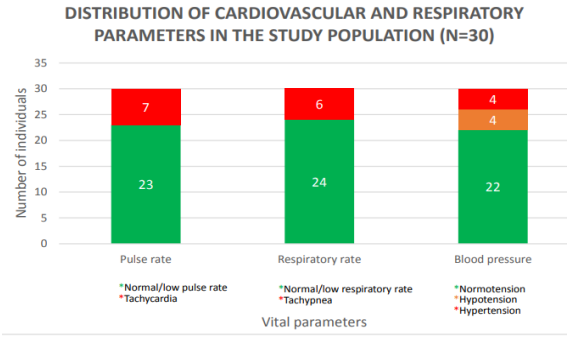
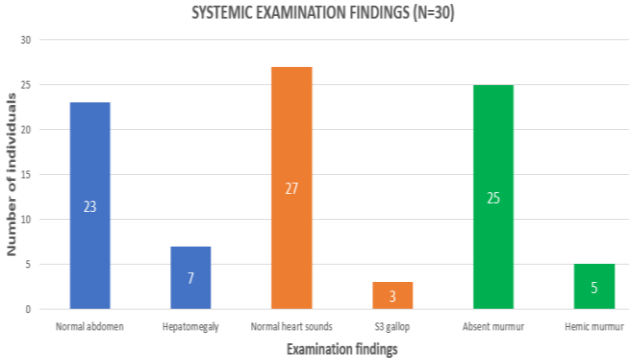


Fig 2: Systemic examination findings among the study population (N=30)



This indicates that while the majority of the study population exhibits normal cardiovascular and respiratory conditions, a notable percentage presentswith vital parameterabnormalitiesand significant findings on systemic examination.

Table 3: Anthropometric parameters among the study population (N=30)

	Characteristics	Frequency	Percentage (%)
Heightforage(z-score) (n=30)			
2to-2	Normal	7	23.33
-2 to-3	Stunting	12	40.00
Lessthan -3	Severestunting	11	36.67
Weightforage (z-score) (n=30)			
2to-2	Normal	10	33.33
-2 to-3	Underweight	8	26.67
Lessthan -3	Severeunderweight	12	40.00
Weightforheight (z-score)6-59months(n=12)			
2to-2	Normal	6	50.00
-2 to-3	Wasting	4	33.33
Lessthan -3	Severewasting	2	16.67
BMI(z-score)5-18years(n=18)			
Morethan2	Obese	0	0.00
2to 1	Overweight	0	0.00
1to-2	Normal	13	72.22
-2 to-3	Thinness	2	11.11
Lessthan -3	Severethinness	3	16.67

Thesefindings highlight theprevalence of malnutrition in the studypopulation, with significant rates of stunting, underweight, and wasting.
The majority of patients (46.67%) were diagnosed 1 to less than 4 years ago and 3.33% had been diagnosed between 7 to 10 years ago.
Table 4 shows the findings on chest Xray with the cardiothoracic(CT) ratio and accordingly classifying the subjects. Table 5 shows the various ECG findings among the study population.
Figure 3 shows the echocardiographic findings among the study population. Thefindings highlight that most patients had a relatively preserved ejection fraction and normal left ventricular function, but a notable proportion showed signs of myocarditis and pericardial effusion.

Table 4: CT ratio as on Chest Xray among the study population

CT ratio	Number	%
0.40 to 0.49	14	46.66
0.50 to 0.59	13	43.33
0.60 to 0.69	3	10.00

Table 5: ECG findings among the study population (N=30#)

ECG finding	Number	%
Normalfinding	17	56.66
Lowvoltage complexes	3	10.00
Sinustachycardia	6	20.00
NonspecificTwavechanges	1	3.33
STeinLeadII	5	16.66
Leftatrialhemiblock	1	3.33
Twave inversion	1	3.33

#: ECGfindingsaremultipleresponses.Thenumberofresponsesis34.

Fig. 3: Echocardiographic findings among the study population (N=30)

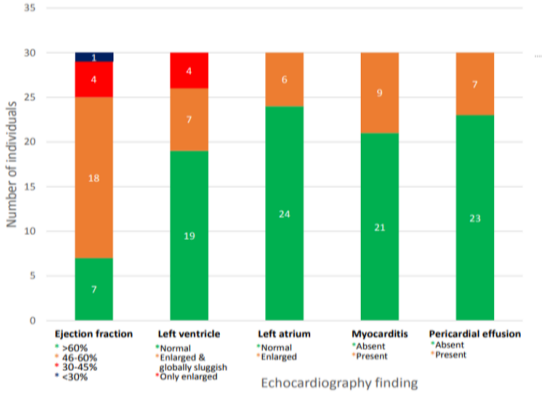


Table 6, 7 and 8 correlates presence of myopericarditis with some study variables and parameters.

Table 6: Correlation of age at diagnosis and weight with myopericarditis

Variable	Myopericarditis absent (n=20)	Myopericarditis present (n=10)	p-value
	Median (IQR)	Median (IQR)	
Age at diagnosis	5.0 (3.5 to 7.0)	2.7 (2.0 to 6.0)	0.100
Weight	20.0 (10.5 to 26.0)	11.6 (10.3 to 16.0)	0.107

Table 7: Correlation of height, body mass index(BMI) and ejection fraction with myopericarditis

Variable	Myopericarditis absent (n=20)	Myopericarditis present (n=10)	Difference	p-value
	Mean ± SD	Mean ± SD		
Height	112.90 ± 24.75	95.10 ± 12.21	17.80 (0.71 to 34.89)	0.042
BMI	14.53 ± 1.59	14.50 ± 2.34	0.03 (-1.45 to +1.51)	0.969
Ejection fraction	55.50 ± 6.16	46.10 ± 12.35	9.40 (2.54 to 16.26)	0.009

Table 8: Simple linear regression model for ejection fraction(EF) with myopericarditis

Variable	Coefficient for EF	Standard error	95% CI	p value
Myopericarditis present	-9.40	3.34	-2.54 to -16.25	0.009

It means that in comparison to a celiac disease child with no myopericarditis, a child with myopericarditis has 9.40 units of ejection fraction lesser (95% CI is -2.54 to - 16.25)(p value is 0.009).

Discussion:

The study evaluated children and adolescents of celiac disease for cardiac comorbidities, revealing several significant patterns.

In our study, out of the 30 participants, the highest were aged 3 to 7 years (36.66%), closely followed by more than or equal to 10 years (26.67%) with a nearly equal gender distribution(53.33% female, 46.67% male). Thisbalanced demographic distribution allows for a comprehensive analysisacross different age groups and genders.

The majority of the study population exhibited normal pulse rate, respiratory rate, and blood pressure for their age, with 76.67%, 80.00%, and 73.33% of individuals respectively falling within the normal range. However, 23.33% showed tachycardia, 20.00% had tachypnea and 26.67% had abnormal blood pressure, hypotension or hypertension, indicating a notable presence of cardiovascular vital parameter abnormalities.

Pallor was the most common clinical sign (40.00%), followed by edema in 16.67%. Presence of hepatomegaly in 23.33%, S3 gallop in 10% and presence of hemic murmur in 16.67% of participants hints about the systemic involvement in celiac disease patients.

Significant rates of stunting (40.00%) and severe stunting (36.67%) were observed, indicating chronic malnutrition. Additionally, severe underweight was prevalent (40.00%) alongside wasting which was also seen in asignificantnumberofparticipantswhileseverewastingandseverethinness was present in 16.67% of the study population highlighting the effect of celiac disease over growth of the individual. A study by Bardella et al. evaluatedbody composition and the impact of a gluten restriction in 29 celiac disease children. Before restricting gluten in diet, children with celiac disease were generally shorter and weighed less compared to matched controls. Mean weight-for-heightz-scoreimprovedfrom-1.5±1.1to-0.1±1.1($p<0.01$), mean height-for-age z-score increased from -0.9 ±1.0 to -0.3 ±1.1 ($p < 0.05$) and the mean BMI z-score increased from -1.0 ± 1.0 to 0.0 ± 1.1 ($p < 0.01$) after one year on the diet[15]. The results goes in hand with the findings of our study that celiac disease affects the somatic growth of an individual.

On Chest X-ray, 10% participants had a CT ratio more than 0.60 indicating cardiomegaly. The reminder of the study population had a normal cardiac silhouette.

On Electrocardiography, 56.66% had a normal tracing while the commonest variation was sinus tachycardia seen in 20% participants. Other variations were in minimal number of participants which also have significant cardiac implications. A population-based cohort study conducted by Singh P et al.in 2022, included 30,000 patients with biopsy-confirmed and serologically validated celiac disease, and 120,000 age- and sex-matched controls from the general population[16]. Over a 10 year follow-up period, the study found that patients with celiac disease had a significantly higher prevalence of cardiac arrhythmias compared to controls. Atrial fibrillation was the most frequently observed arrhythmia. The hazard ratio (HR) for developing arrhythmia was higher in the celiac disease cohort.

Echocardiography revealed that while most patients had normal leftventricular function (63.33%), a significant portion exhibited myocarditis (30.00%) and pericardial effusion (23.33%). The correlation analysis showed that myopericarditis had lower ejection fractions. In the study, 60% of participants exhibited mild left ventricular systolic dysfunction, with an ejection fraction ranging from 46% to 60%.Additionally, one participant (3.33%) demonstrated severe left ventricular systolic dysfunction, with an ejection fraction below 30%.

Fonager K et al.'s found in 1999 a high incidence rate of cardiomyopathy in 86 per 100000 person years between the years of 1987 to 1992[17]. This suggests that cardiac comorbidities are prevalent in celiac patients.

Rubio-Tapia A et al. conducted a study in 2018 to evaluate the risk of heart failure in celiac disease. The study included 8,846 patients with biopsy- confirmed celiac disease and 43,474 age- and sex-matched controls. The findings revealed a hazard ratio of 1.46 (95% CI, 1.17-1.82) for heart failure in patients with celiac disease[18]. It corresponds to the finding in our study that 76.67% of patients have left ventricular systolic dysfunction (mild 60%, moderate 13.33% and severe 3.33%).

Mizrahi et al. conducted a study in 2020 to examine the prevalence of pericarditis in celiac disease. The study included 13,223 patients with biopsy- confirmed celiac disease and 66,115 age- and sex-matched

controls. The findings revealed that patients with celiac disease had a higher incidence of pericarditis compared to the control group. The hazard ratio for pericarditis in cases was 1.82 (95% CI, 1.45-2.29)[19]. This correlates with our study wherein 23.33% of the study population had features suggestive of pericardial involvement.

Polat et al. conducted a study in 2008 to examine systolic dysfunction and other cardiac abnormalities in celiac disease using echocardiographic evaluation. The study involved 45 celiac disease cases and 45 healthy age- and sex-matched controls. The results showed that the mean left ventricular ejection fraction (LVEF) in cases was 66.3% ±4.7%, compared to 70.0% ± 4.9% in the control group, with this difference being statistically significant ($p < 0.01$). Additionally, the study found that children with celiac disease had significantly lower LVEF and fractional shortening (FS) compared to their healthy peers[20].

In the group with myopericarditis present, the median age at diagnosis is lower(2.7years) compared to the group with myopericarditis absent (5 years), the median weight is lower in the group with myopericarditis present (11.6kg) compared to the group with myopericarditis absent (20kg) and the mean BMI is nearly identical between the groups with p value of 0.100, 0.107 and 0.969 respectively. The p-values indicates that the difference of these variables between the two groups is statistically insignificant.This suggests that there is no strong evidence to conclude that the age at diagnosis, weight or BMIdiffers significantly between the two groups based on the findings. Mean height is higher in the group without myopericarditis (112.9cm) in comparison to one with myopericarditis (95.1cm). The p-value of 0.042 indicates that this difference is statistically significant. This says the height differs significantly between the two groups.The difference in ejection fraction is significant between the groups, with the group without myopericarditis (55.5%) having a higher mean ejection fraction compared to the group with myopericarditis (46.1%).

Alinear regression between presence of myopericarditis and ejection fraction yields a negative coefficient of -9.40 which indicates that having myopericarditis is associated with a significantly lower ejection fraction (9.40 units). The p-value of 0.009 indicates that this association is statistically significant, suggesting a strong likelihood that the observed association is not due to random chance.

Conclusions:

The study's findings emphasises the urgent need for routine cardiovascular monitoring in celiac disease.The high prevalence of tachycardia, myocarditis, pericardial effusion, and associated left ventricular dysfunction, along with other cardiac abnormalities, indicates that celiac disease has a significant impact on cardiac health.

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