Carotid intimal thickness and response to gluten-free diet: A prospective study in children with celiac disease

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ABSTRACT

Background: Carotid intimal-medial thickness (CIMT) has recently emerged as one of the early markers of atherosclerosis and is helpful in providing direct evidence in comparison to traditional biochemical screening parameters. **Objective:** The objective of the study was to determine the change in the CIMT in children with celiac disease (CD) aged 1–14 years after 6 months of gluten-free diet (GFD). **Materials and Methods:** A total of 31 consecutive children with newly diagnosed CD (anti-tissue transglutaminase antibody titer of >10 U/L and intestinal biopsy histology of either Marsh Grade 3B or 3C) were enrolled in the study. CIMT was measured at the time of diagnosis and after 6 months follow-up on GFD by a single experienced radiologist who was blinded to the participant's case status and risk factors. **Results:** The mean age of enrolled cases in our study was 7.58±3.38 years. The mean CIMT among enrolled children before GFD (0.0523±0.0069 cm) and after 6 months of GFD (0.0537±0.0063 cm) was greater than that of expected CIMT for this age (0.0411±0.5 cm). After 6 months of GFD, mean values on the right side (anterior wall, posterior wall, and mean; p=0.27, 0.794, and 0.557, respectively) or the left side (anterior wall, posterior wall, and mean; p=0.122, 0.063, and 0.078, respectively) were not statistically significantly. **Conclusion:** CIMT among children with CD was increased at enrolment but did not decrease significantly after 6 months of GFD. Further, studies are needed to be conducted with longer duration of follow-up for more insight into the subject.

Key words: *Carotid intimal thickness, Celiac disease, Gluten-free diet*

Higher prevalence of cardiovascular diseases such as autoimmune myocarditis, cardiomyopathy, ischemic heart disease, arrhythmias, cerebrovascular diseases, and sudden death occur is known in those diagnosed of celiac disease (CD) in comparison to the general population [1-9]. This may be attributed to the chronic systemic inflammation, autoimmune process, accelerated atherosclerosis, and unfavorable biochemical profile [10-13]. Metabolic abnormalities such as raised C-reactive protein level, increased plasma homocysteine level, and deranged lipid profile (total/HDL cholesterol) increase the risk of cardiovascular morbidity and mortality in the CD patients [10,14,15]. Atherosclerosis may have an early onset and progressive course in the presence of various risk factors.

Carotid intimal medial thickness (CIMT) has emerged as one of the early markers of atherosclerosis and gives more direct evidence as compared to traditional biochemical screening markers like lipid profile [16-20]. The previous studies on CIMT in CD patients have shown a significant higher reduction after the introduction of gluten-free diet (GFD) [10,21]. These results suggested that withdrawal of gluten in the diet of CD may have a beneficial effect on the atherosclerotic risk factors. With the growing morbidity and mortality due to cardiovascular diseases in the general population, it has become important to evaluate the patients with a higher risk profile like the CD early in life to enable early intervention and prevention. Hence, we planned to evaluate the change in the CIMT in children with CD aged 1–14 years after 6 months of GFD.

MATERIALS AND METHODS

This prospective observational study was conducted in the department of pediatrics at a tertiary care hospital over 18 month's duration from November 2018 to March 2019. The study was approved by the Institutional Ethical Committee. A minimum of 26 children was required to complete the study to detect a mean difference of 0.024 in pre- and post-GFD CIMT, with 90% power of study and 5% level of significance on the basis of the study by De Marchi *et al.* [10]. A total of 31 children were enrolled with an expected 20% loss to follow up.

Newly diagnosed CD between 1 and 14 years from outpatient department and pediatric wards with clinical symptoms or asymptomatic children with a family history with positive serology (IgA anti tTG antibodies or IgG anti-DGP antibodies in IgA deficiency) and biopsy findings (villous atrophy Marsh 3 stage) was enrolled for the study [22]. Children diagnosed with any other

associated known chronic infections (tuberculosis, inflammatory bowel disease, etc.); inflammatory diseases (vasculitis, connective tissue disorders, etc.); chronic diseases such as rheumatological and cardiac diseases; and drugs affecting serum iron and lipid levels (statins, steroids, etc.) or conditions with hyperlipidemia (nephrotic syndrome, congenital hyperlipidemias, Cushing's disease, diabetes mellitus, and hypothyroidism) were excluded from the study. An informed written consent was obtained from parents or guardians of all children enrolled in the study. The clinicodemographic details along with biochemical investigations were recorded in case record pro forma at the time of enrolment.

CIMT was measured with the standard technique at the time of enrolment and after 6 months of GFD in a quiet room at a comfortable temperature, after 15–20 min of rest by a single experienced radiologist, blinded to the participant's case status and risk factors. High resolution B-mode ultrasonography with a 7.5 MHz linear array transducer was used. CIMT was measured from the common carotid artery 10–20 mm below the carotid bulb on each side of neck. The average of three consecutive measurements of maximum far and near wall thickness up to the three decimal places in mm was obtained on each side and the mean CIMT was calculated as average of the right and the left values.

The data were analyzed using the SPSS version 21.0. Continuous variables were presented as mean ± SD. Data were checked for normality before statistical analysis. Quantitative variables were compared using paired t-test/Wilcoxon test across follow-up. Qualitative variables were correlated using Chi-square test/Fisher's exact test. Pearson correlation coefficient/Spearman rank correlation coefficient was used to assess the association of various parameters with each other. For all statistical tests, $p<0.05$ was statistically significant.

RESULTS

The mean age of enrolled children in our study was 7.58±3.38 years. A majority of the children (80.64%) were between 4 and 12 years of age (Table 1). There was no statistically significant difference in age or sex distribution of enrolled children. A majority of the cases had an onset of symptoms at age <8 years (76.92% of males; 72.22% of females) with mean age of onset at 5.89±3.35 years and no difference in both genders (p=0.19). Majority of the children (53.86% of females and 66.66% of males) were symptomatic for 6–24 months before diagnosis with a mean duration being 20.87±21.52 months.

A total of 83.87% of the cases presented with typical gastrointestinal (GIT) symptoms. Diarrhea (67.74%) and pain abdomen (48.39%) were the most frequent GIT symptoms and paleness of body (35.48%) and not gaining weight (45.16%) were the predominant non-GIT symptoms before GFD. Other GIT symptoms included vomiting (83.87%), constipation (19.35%), abdominal distension (6.45%), and anorexia (38.71%) (Table 1). There were two cases of diabetes mellitus. None of the included children had neurological, dermatological, or skeletal symptoms.

Table 1: Baseline clinical characteristics of enrolled children with CD

Parameter	Percentage (n)	p-value
Age of enrolment (years)		
<4	16.13 (5)	0.12
4–12	80.64 (25)	
>12	3.23 (1)	
Age of onset of symptoms (years)	Male, n (%); female, n (%)	
<4	2 (15.38); 8 (44.44)	0.19
4–8	8 (61.54); 5 (27.78)	
9–12	3 (23.08); 4 (22.22)	
>12	0 (0.00); 1 (5.56)	
Duration of illness (months)	Female: male	
<3	2 (15.38); 2 (11.11)	0.962
3–6	2 (15.38); 2 (11.11)	
6–12	3 (23.08); 6 (33.33)	
12–24	4 (30.78); 6 (33.33)	
>24	2 (15.38); 2 (11.12)	
GIT symptoms, n (%)	15, 48.39	
Non-GIT symptoms	19, 61.29	
Not gaining weight	14, 45.16	
Hematological (paleness of body)	11, 35.48	
Endocrinal (DM)	2, 6.45	
TTG titer (U/L) range, n (%)		
10–50	7, 22.58	
50–100	3, 9.68	
100–500	20, 64.52	
>500	1, 3.23	

CD: Celiac disease, GIT: Gastrointestinal

Among the enrolled children, many were malnourished (51.61% in weight, 64.52% in height, and 38.71% in body mass index) with scores <3rd centile before GFD. A majority (64.52%) of the cases had high titers of anti-tTG IgA antibodies (100–500 U/L) with mean (SD) 145.15 (141.08) and median: 145 (range: 10.53–800.4). Most of the cases had modified Marsh staging (grade of 3B [87.1%] on D2 biopsy).

As shown in Fig. 1, the mean CIMT before (0.0523±0.0069 cm) and after 6 months of GFD (0.0537±0.0063 cm) were greater than that of expected mean CIMT of the study group (0.0411±0.5 cm). The mean CIMT in the right side (anterior wall, mean posterior wall, and combined) mean values was not statistically lower from baseline after 6 months of GFD (p=0.27, 0.794, and 0.557, respectively). Similarly, the mean CIMT in the left side (anterior wall, posterior wall, and combined) was also not statistically significantly lower from baseline after 6 months of GFD (p=0.122, 0.063, and 0.078, respectively).

DISCUSSION

CD is common in pediatric practice with high risk of cardiovascular morbidity. Changes in CIMT have not been evaluated in children with CD after GFD therapy. In our study

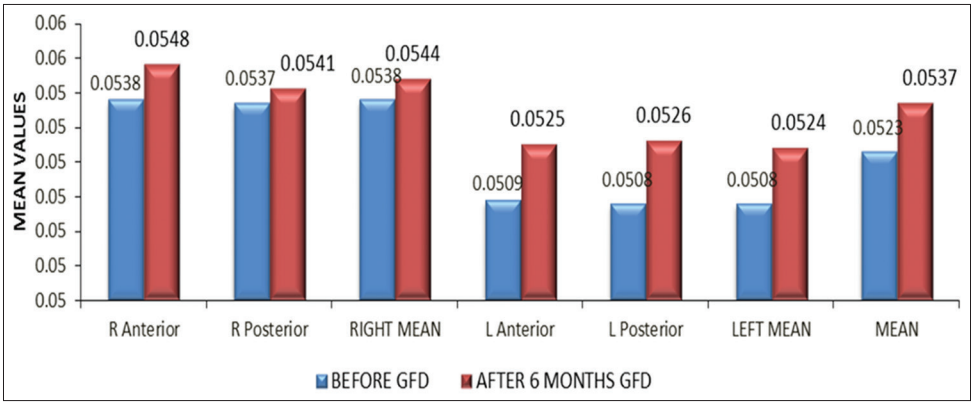

Figure 1: Carotid intimal medial thickness of enrolled children before and after 6 months of gluten-free diet

of 31 children with newly diagnosed CD, we found high mean CIMT before (0.0523±0.0069 cm) and after 6 months of GFD (0.0537±0.0063 cm) in comparison to expected CIMT for this age (0.0411±0.5 cm). However, there was no statistically decrease in mean CIMT levels after 6 months of GFD therapy.

We compared our results with the previous study by Pitocco *et al*. who studied cases of CD and Type-I DM among the age group of 35–40 years and concluded that CD patients had greater CIMT as compared to healthy controls (0.048±0.016 cm vs. 0.031±0.007 cm; p<0.001) [21]. Similar results were reported by De Marchi *et al*. in CD in the age group of 23–41 years where CIMT was increased among the cases in comparison to controls at baseline (0.082±0.011 vs. 0.058±0.012; p<0.005) and reported a decrease in CIMT (0.064±0.010 cm) after 6–8 months of gluten abstinence [10]. Demir *et al*. in children between 6 and 18 years of age with CD did not report any statistically significant difference in CIMT (p=0.557) between cases (0.43±0.08) and controls (0.42±0.04) [23].

However, in our study, there was no decrease in CIMT (0.0537±0.0063 vs. 0.0411±0.5 cm) even after 6 months of GFD as compared to an adult study [10]. This may be due to difference in the study population and an expected increase in CIMT with age in children as reported by Koçyiğit *et al*. in their study [24]. However, the baseline CIMT remained much higher than the mean values at different age groups. The outcome of a longer duration of follow-up needs to be further analyzed. Watanabe *et al*. in their study on Japanese population concluded that the annual CIMT change was associated with age, and not with cardiovascular risk factors, such as diabetes and hypertension [25].

The study had a few limitations. We could not demonstrate any decrease in CIMT after GFD for 6 months. The study had a small sample size and was conducted for shorter duration.

CONCLUSION

CIMT among the CD children was increased at baseline without significantly decreasing even after 6 months of GFD in our study but still remaining higher than baseline. Further studies with longer duration of follow-up are needed for more insight into the subject.

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