Original Article

Carotid intimal medial thickness in children with celiac disease

Y M Bhavika[1], Vivek Dewan[2], Namrita Sachdev[3], T P Yadav[2], Hema Mittal[4], Ajeet Kumar Yadav[5], Surat Nabum[1]

From [1]Post Graduate Student, [2]Professor, [4]Assistant Professor, [5]Senior Resident, Department of Pediatrics, [3]Associate Professor, Department of Radio Diagnosis, Postgraduate Institute of Medical Education and Research and Dr. Ram Manohar Lohia Hospital, New Delhi, India

Correspondence to: Dr. Y M Bhavika, Department of Pediatrics, Postgraduate Institute of Medical Education and Research and Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001, India. E-mail: bhavsym@gmail.com

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ABSTRACT

Introduction: Increasing cardiovascular risk in celiac disease (CD) may be attributed to the chronic systemic inflammation and unfavorable biochemical profile leading to accelerated atherosclerosis. Carotid intimal medial thickness (CIMT) has emerged as a direct marker of the early atherosclerosis as compared to traditional biochemical markers. O**bjectives:** The aim of this study was to evaluate the CIMT in children with CD aged 1–16 years. **Materials and Methods:** A cross-sectional observational study was conducted at the department of Pediatrics and Radio Diagnosis in a tertiary care hospital of New Delhi. Thirty-six children with CD with age- and sex-matched controls were enrolled. CIMT for the anterior and posterior walls on each side was measured, and the mean CIMT was obtained for all the enrolled children. **Results:** The mean right-sided CIMT was significantly higher in cases (0.053±0.009 cm vs. 0.039±0.007 cm, p=0.000). The mean left-sided CIMT did not significantly differ between the groups (0.051±0.009 cm vs. 0.048±0.055 cm, p=0.702). The mean CIMT (right and left together), although higher in Celiacs, was not significantly different from controls (0.052±0.008 cm and 0.044±0.029 cm, p=0.114). However, a significant positive correlation between the age of the patients, age at the onset of symptoms, and CIMT was noted. **Conclusion:** Although we could not demonstrate statistically significant results, the mean CIMT and the right-sided measurements were significantly higher in cases than in controls.

Key words: *Atherosclerosis, Carotid intimal medial thickness, Celiac disease*

Celiac disease (CD) is a chronic small-bowel enteropathy with an underlying autoimmune mechanism precipitated by exposure to dietary gluten in genetically predisposed people [1]. 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 the adults in Western and Northern India, respectively [2]. Increased risk of death due to cardiovascular diseases among the celiac patients as compared to the general population is recently evident by various studies [3,4]. This may be attributed to the chronic systemic inflammation, autoimmune process, and unfavorable biochemical profile, leading to early and accelerated atherosclerosis [5].

Although atherosclerosis manifests clinically in the middle and late adulthood, it has a prolonged insidious course with onset early in life. Coronary angiography has been the cornerstone of diagnosis in the past; its usefulness is limited by the fact that it is invasive and restricted to analyzing the lumen. Since early atherosclerosis involves endothelium of many arteries, noninvasive tests such as ultrasonography enable the evaluation of arterial wall rather than just the lumen and thus well suited for sequential follow-up and repeated evaluations, especially in the pediatric population. Carotid intimal medial thickness (CIMT) has emerged as a marker of early subclinical atherosclerosis which gives more direct evidence as compared to traditional biochemical markers [6,7] and has a better correlation to cardiovascular morbidity and mortality. As it is important to evaluate the patients with a higher risk profile like the celiac patients early in life to enable early intervention and preventive measures, we planned the first such study from India to evaluate CIMT in children with CD aged 1–16 years in comparison to age- and sex-matched controls.

MATERIALS AND METHODS

A cross-sectional observational study was conducted from November 2015 to March 2017 in the department of Pediatrics and Radio Diagnosis in a tertiary care hospital of New Delhi. The sample size was calculated on the basis of a previous study by De Marchi *et al*. [5] conducted in adults to detect 20% difference for CIMT between the groups (CIMT in healthy controls – 0.058 cm). With the standard deviation (0.011, 0.012), power of 90%, and an alpha level of 0.05, a total of 40 children (20 in each group) were required to complete the study. For the purpose of the study, CD was defined based on the World Gastroenterology Organization Guidelines for CD 2012 [8].

Of the 147 celiac patients screened for inclusion in the study, 36 children newly diagnosed with CD with anti-tissue transglutaminase (tTG) antibody titer of >10 upper limit normal and an intestinal biopsy finding of either Marsh stage 3B or 3C changes were enrolled into the study with a primary objective to measure the CIMT. Children who were already diagnosed and on treatment with a gluten-free diet (GFD) before the start of the study were not included in the study, as GFD 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. Thirty-six age and sex-matched controls were enrolled among the children attending the outpatient departments for immunization and siblings of the children attending the department for minor illnesses. Ethical clearance was obtained from the hospital committee, and informed written consent was obtained from all the parents/guardians before the enrolment.

The demographic details, anthropometric measurements, and the investigations, pertaining to the diagnosis of CD such as anti-tTG immunoglobulin A (IgA) antibody titers and intestinal biopsy findings, were recorded. The enrolled children were studied under standardized conditions in a quiet room at a comfortable temperature. The measurements were made with high-resolution B-mode ultrasonography with a 7.5 MHz linear array transducer, after a rest of 15–20 min by a single experienced radiologist, blinded to the participant's case status. The IMT was measured from the common carotid artery 10 mm to 20 mm below the carotid bulb on each side as shown in Fig. 1. The averages of three consecutive measurements for the anterior and posterior walls were obtained on each side to decrease intra-observer variation. The mean CIMT was calculated on each side, and then, the final mean for the case was calculated as the average of the right and the left values.

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables were presented as mean±SD, and categorical variables were presented as absolute numbers and percentage. Data were checked for normality before the statistical analysis. 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. For within the group comparisons, the Spearman correlation was performed to determine the relationship between the various variables and CIMT. For all statistical tests, a $p<0.05$ was taken to indicate a significant difference.

RESULTS

Cases and controls were comparable in their age distribution with a mean age of 7.72±3.26 years and 7.56±3.18 years, respectively. The male:female ratio was 5:4 in both the groups. The mean age at the onset of symptoms among the cases was 5.86±3.09 years. Totally, 50.0% (18) of the cases and 2.8% (1) of the controls had wasting ($p<0.001$) and 61.1% (22) of the cases and 5.6% (2) of the controls had stunting ($p<0.001$).

As listed in Table 1, CIMT measurements on the right side, both in the anterior as well as posterior walls were significantly more in cases than in controls. However, on the left, only the posterior wall CIMT values were significantly higher among the cases. Furthermore, the mean CIMT values among the cases and the controls (0.052±0.008 cm vs. 0.044±0.029 cm) did not differ significantly between the cases and controls.

When the data were analyzed for correlation between different demographic variables and CIMT, a significant correlation was found between age of the patients, age at onset of the symptoms, and CIMT values in cases with correlation coefficients of 0.520 and 0.437, respectively ($p=0.001$, $p=0.008$). We could not find any significant correlation between CIMT and variables such as sex, anthropometric parameters, duration of illness, and tTG titers among the cases.

DISCUSSION

CD is a chronic gastrointestinal disease with implications on various organ systems including the cardiovascular system. Because the treatment involves a major lifestyle change, a therapeutic approach should not only emphasize the current but also predict and prevent the later complications. It is unique even among the other chronic diseases because of its early onset and association with specific comorbidities. Traditional risk factors for cardiovascular disorders include the presence of metabolic

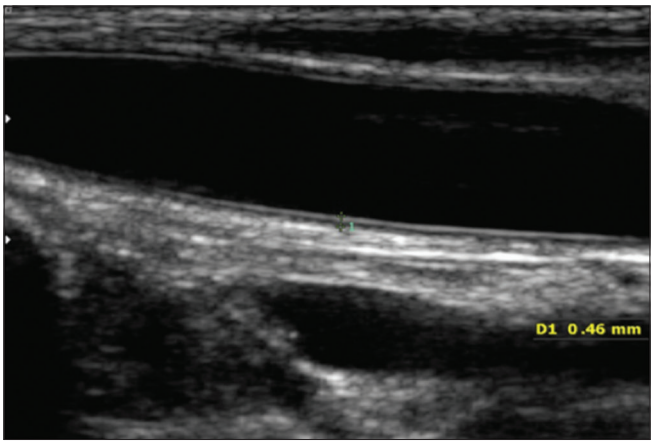

Figure 1: Carotid Doppler showing measurement of intimal medial thickness

Table 1: Carotid intimal medial thickness among the cases and controls

Carotid intimal medial thickness (cm)	Cases (Mean±SD)	Controls (Mean±SD)	p value
Right anterior	0.054±0.010	0.037±0.008	0.000
Right posterior	0.053±0.010	0.040±0.008	0.000
Right mean	0.053±0.009	0.039±0.007	0.000
Left anterior	0.052±0.010	0.047±0.044	0.479
Left posterior	0.050±0.010	0.038±0.008	0.000
Left mean	0.051±0.009	0.048±0.055	0.702
Mean	0.052±0.008	0.044±0.029	0.114

SD: Standard deviation

syndrome, inflammatory mediators, and other metabolic derangements. Clustering of risk factors is evident in childhood and persists into young adulthood [9-12]. Although most celiac patients experience clinical remission with treatment, endoscopic abnormalities and histologic inflammation may persist for many years in more than half of them even with good dietary compliance [13]. Cardiovascular disease is one of the leading causes of death among patients with CD [14-16].

Atherosclerosis is a complex chronic inflammatory process. Vascular involvement in atherosclerosis begins with endothelial dysfunction [17] which has been demonstrated in the previous studies in patients with CD [18]. T-lymphocytes responsible for mucosal inflammatory response are not limited to the intestinal wall but are also found in peripheral circulation [19,20], which through cytokines may activate processes leading to atherosclerosis. Increased risk of atherosclerosis in CD patients could also be explained by the contribution of gliadin peptides in the oxidative modification of low-density lipoprotein, leading to the conversion of simple fatty streaks into complicated atheromas [21-23].

Although atherosclerosis manifests clinically in the middle and late adulthood, it is a chronic process with the prolonged insidious course and has its onset early in life. Various autopsy studies have demonstrated fatty streaks, documenting a strong relation between risk factors and coronary atherosclerosis in young people thus demonstrating the ubiquity of atherosclerotic process and clustering of risk factors in pediatric population which persists into adulthood. The severity of asymptomatic coronary and aortic atherosclerosis increases as the number of cardiovascular risk factors increases [24-31].

Ultrasonographic examination of peripheral arteries such as carotid artery enables the evaluation of arterial wall rather than just the lumen. CIMT is a direct measure of carotid atherosclerosis but more importantly, an indirect measure of generalized atherosclerosis. Thus, it can be considered as a validated surrogate cardiovascular endpoint. Early preventive measures, therefore, can be undertaken to slow the atherosclerotic process and delay cardiovascular disease.

Only three studies evaluating CIMT in CD have been published till date, but none of them are from the Indian subcontinent. In 2011, Pitocco *et al.* [32] studied 120 adult patients with CD and Type 1 diabetes mellitus with an age range of 35–40 years. After evaluation of all the patients with ultrasonography, they concluded that celiac patients had greater CIMT as compared to healthy controls. Similarly, in 2013, De Marchi *et al.* [5] evaluated 20 patients with CD aged 23–41 years with CIMT. At the diagnosis, CIMT was found to be significantly higher among the celiac patients with a mean of 0.082±0.011 cm as compared to controls with a mean of 0.058±0.012 cm. They also found a significant improvement in the same after 6–8 months of gluten abstinence with a mean CIMT of 0.064±0.010 cm. Thus, CIMT was found to be a valuable tool to assess the potentially increased risk of early atherosclerosis among adults with CD.

Recently in 2016, Demir *et al.* [33] from Turkey studied 37 celiac patients aged between 6 and 18 years. Although they did not find any significant difference between cases and controls, they demonstrated a positive association between tTG IgA antibody positivity and CIMT with a significant difference in CIMT between tTG negative and positive patients. They also demonstrated a decrease in CIMT with strict gluten restriction to conclude that gluten withdrawal has a beneficial effect on premature atherosclerosis.

In our study, the children were aged between 1 and 16 years. The mean CIMT did not demonstrate any significant difference between the groups although it was increased in cases as compared to controls by 0.008 cm. Pitocco *et al.* [32] observed a mean CIMT of 0.048±0.016 cm and 0.031±0.007 cm, respectively ($p<0.001$). De Marchi *et al.* [5] in 2013 observed a mean CIMT of 0.082±0.011 cm and 0.058±0.012 cm, respectively ($p<0.005$). However, in the study by Demir *et al.* [33], no difference was found between the cases and controls with a mean CIMT of 0.041±0.006 cm and 0.042±0.004 cm, respectively ($p=0.111$).

Among the cases in our study, a significant $p=0.001$ with a correlation coefficient of 0.520 was also observed between the age of the patients and mean CIMT. Similarly, $p=0.008$ was observed with a correlation coefficient of 0.437 between the age at the onset of illness and the mean CIMT. Thus, CIMT was seen to increase with the increasing age of the patients and also with the increasing duration of illness before the diagnosis. Although Pitocco *et al.* [32] and De Marchi *et al*. [5] did not describe any such correlation with demographic or clinical parameter, Demir *et al.* [33] found a correlation between CIMT and anti-tTG antibody titers. However, our study failed to demonstrate any statistically significant association between CIMT and anti-tTG antibody titers. Since we had only included celiac patients with intestinal biopsy showing Marsh grade 3B and 3C changes, our cases do not represent the whole population of children with CD. Re-evaluation after treatment with the institution of GFD could not be done, as ours was a cross-sectional study which could have given us more insight into the topic.

CONCLUSION

The mean CIMT though higher among the cases did not show a statistically significant difference between cases and controls. However, we could demonstrate CIMT values on the right side to be significantly higher among the cases. A significant positive correlation between the age of the patients, age at the onset of symptoms, and CIMT was also noted in cases. Further studies are needed to evaluate the significance of CIMT measurement in the pediatric population with CD.

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