

Lipid Profile in Children with Celiac Disease: Effect of Six Months Gluten Free Diet

Shivani Deswal¹, Surat Nabum², Vivek Dewan³, Shikha Singh⁴, Rahul Tiotia⁵, Vani Narayani K⁶, CP Yadav⁷

ABSTRACT

Introduction: Cardiovascular disease is one of the leading causes of death among adult celiacs. Increased risk is attributed to unfavourable cholesterol profile. Studies on lipid profile among celiacs have shown variable results. Effect of gluten free diet (GFD) on cardiovascular risk profile is further controversial. Knowledge among children can help in risk stratification and timely modification of diet if needed. Current study objective was to record the lipid profile among children with celiac and the impact of six months of gluten free diet on it.

Material and methods: In this single arm pre and post interventional study, newly diagnosed symptomatic children 1-14 years with Tissue Transglutaminase (tTG) IgA antibody positive and biopsy proven (Marsh 3) celiac were enrolled. Sample size of 31 was calculated as per TC and HDL reference levels. Fasting Lipid profile was evaluated at baseline and at six months of GFD. Children with diabetes, hypothyroidism, nephrotic syndrome, congenital hyperlipidaemia and on drugs causing hyperlipidaemia were excluded. The data analysis was done using Statistical software R and Stata 15.0. Quantitative variables were compared using Paired T test/Wilcoxon test. Qualitative variables were correlated using Chi-Square test/Fisher's exact test.

Results: Median age of children was 8 years (5-10 years). Median age at onset of symptoms was 6 (3.15 -8.75) years and median duration of illness prior to diagnosis was 12 (7.5-24) months. 83.87% presented with typical GI symptoms. Mean Total cholesterol (TC) was 131.8±39.7 mg/dl, mean HDL cholesterol was 41.2±12.6 mg/dl, mean Triglycerides was 92.0±35.5mg/dl and mean LDL was 75 ± 32.3 mg/dl at diagnosis. Average increase in HDL after GFD was 13 (4.9 to 21.3) mg/dl. TC/HDL ratio was decreased significantly after GFD {-0.5 (-0.9 to -0.03)}.

Conclusion: Children with celiac have a normal lipid profile. GFD for six months increases HDL-C plasma concentration and lowers TC/HDL ratios.

Key words: Metabolic; cardiovascular; Atherosclerosis; Gastroenterology; Paediatric

factors increase.⁵⁻⁷ Early screening and preventive measures therefore need to be undertaken. Coronary angiography is not applicable in the paediatric subset and B-mode ultrasonographic evaluation of carotid intimal medial thickness is yet to be standardised as a screening tool. Serum cholesterol level is a well-known risk factor. LDL-cholesterol has a critical importance in atherogenesis but HDL-cholesterol has a greater significance as a protective factor. Different studies have shown variable results with respect to lipid profiles in patients with celiac. They are found to be most commonly associated with hypocholesterolaemia with low levels of Total Cholesterol, LDL-Cholesterol and HDL-Cholesterol.⁸⁻¹² The impact of Gluten free diet (GFD) on lipid profiles is further unclear. In few studies GFD has shown to improve lipoprotein profile in celiac patients. However in other studies it has been attributed to worsen cardiovascular risk profile due to high content of saturated fat.¹³⁻¹⁵ Hence, we tried to evaluate lipid profile among children with celiac at diagnosis and at 6 months of treatment with GFD assuming this knowledge will give insight into the biochemical cardiovascular risk profile and guide timely modification of gluten free diet if required.

MATERIAL AND METHODS

Single arm pre and post interventional study was conducted on paediatric population (1- 14 years) presenting to paediatric gastroenterology clinic between 1st Nov 2016 and March

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INTRODUCTION

Celiac disease is a complex autoimmune genetic disease, with prevalence of around 1% in the Indian population. Cardiovascular disease is one of the leading causes of death among adult patients with celiac disease.^{1,4} Increased cardiovascular risk in celiac has been attributed to chronic inflammation, autoimmunity, accelerated atherosclerosis and unfavourable cholesterol profile [Fig1]. Atherosclerosis has onset early in life and severity of asymptomatic atherosclerosis increases as the number of cardiovascular risk

2018 as a part of the larger study approved by the ethical review committee of the hospital.

Sample Size: Sample size was worked up for TC and HDL. By assuming TC level as 169.2 ± 35.3 mg/dl and 188.8 ± 32.8 mg/dl before and after gluten free diet respectively, correlation between pre-post measurement as 0.4, alpha as 5%, power as 80%, we were requiring 31 subjects. Similarly for HDL, we assumed average HDL level as 45.8 ± 13.3 mg/dl and 55.1 ± 13.6 mg/dl before and after gluten free diet respectively, correlation between pre and post measurement as 0.4, alpha as 5% and power as 80%, we required 21 individual to assess the effect of gluten free diet on HDL level.¹⁴ Hence, we recruited 31 children with celiac at diagnosis and at six months GFD.

Case definition of celiac: Children with clinical symptoms with positive Tissue Transglutaminase IgA antibodies and evidence of villous atrophy (Marsh staging 3) on duodenal biopsy.¹⁶

Exclusion criteria: Children diagnosed with conditions associated with hyperlipidaemia like nephrotic syndrome, congenital hyperlipidaemias, Cushing's disease, diabetes mellitus, hypothyroidism or on drugs affecting serum lipid levels (statins, steroids) were excluded.

All the consecutive children with fulfilling the case definition were enrolled for the study. Informed written consent was obtained from parents or guardians. All clinico-demographic details were noted in a predesigned Performa. Anthropometric measurements including weight, height and BMI were recorded using standard methods. After obtaining details, a total of 5 ml of venous blood from a peripheral vein was drawn after overnight fasting (minimum 8 hours) using standard technique at diagnosis and after 6 months of GFD. They were evaluated for compliance to GFD by detailed dietary history and clinical evaluation by consultant.

The samples were analysed for following.

Serum lipid profile

Total serum cholesterol and serum triglycerides levels were measured using cholesterol oxidase and colorimetric methods respectively.

HDL cholesterol levels were measured by direct non-immunological assay.

LDL cholesterol levels were calculated by Friedwald (1972) formula [$LDL = TC - HDL - TG/5.0$ (mg/dL)].

Serum Albumin (g/dl)

C-Reactive protein (mg/dl)

Laboratory values were analysed using standard reference values for age and sex.^{17,18}

STATISTICAL ANALYSIS

The data was entered in MS EXCEL spreadsheet, and analysis was done using Statistical software R and Stata 15.0. Data was checked for normality before statistical analysis. Normality of data was tested by Kolmogorov-Smirnov test. Continuous variables were presented as mean \pm SD or median (P25- P75). Categorical variables were presented as absolute numbers and percentage. If the

normality was rejected then non parametric test was used. 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, a p value less than 0.05 was considered as significant.

RESULTS

In this prospective observational cohort study, 33 newly diagnosed cases of celiac disease were enrolled initially. Two cases of Type I diabetes mellitus were excluded. 31 completed the study. Median age of children was 8 years. 80.64% (n=25) were between 4 to 12 years of age. All of them had anti tTG IgA positivity with 87.1% (n=27) having modified Marsh grade 3b and 12.90% (n=4) Marsh 3c in intestinal biopsy. Male: Female ratio was 1.3:1 (p =0.36). Median age at onset of symptoms was 6 (3.15 -8.27) years and median duration of illness prior to diagnosis was 12 (7.5-24) months.

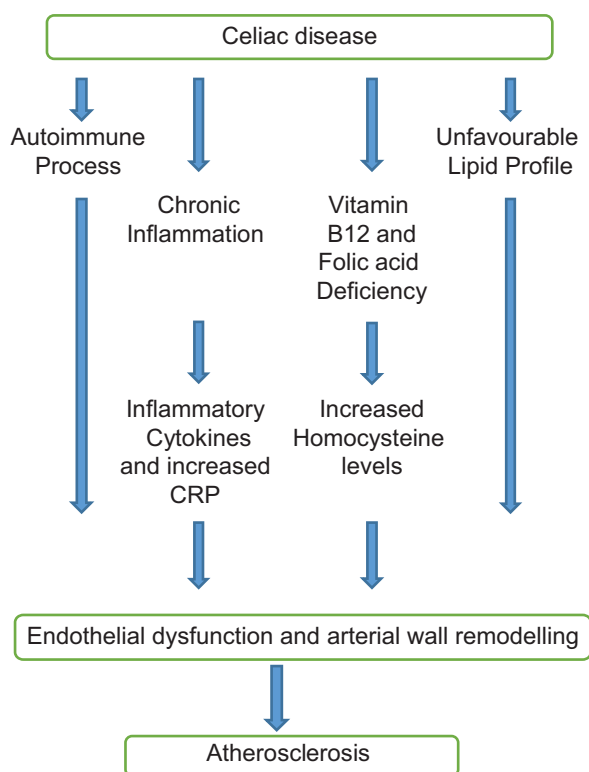


Figure-1: Etiopathogenesis of atherosclerosis in celiac disease^{5,6,7}

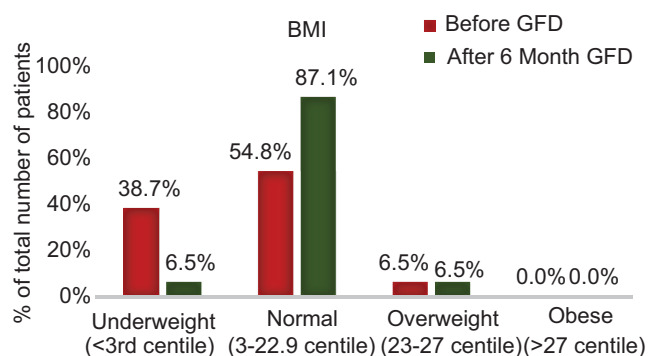


Figure-2: BMI (kg/m²) at diagnosis and after six months of GFD.

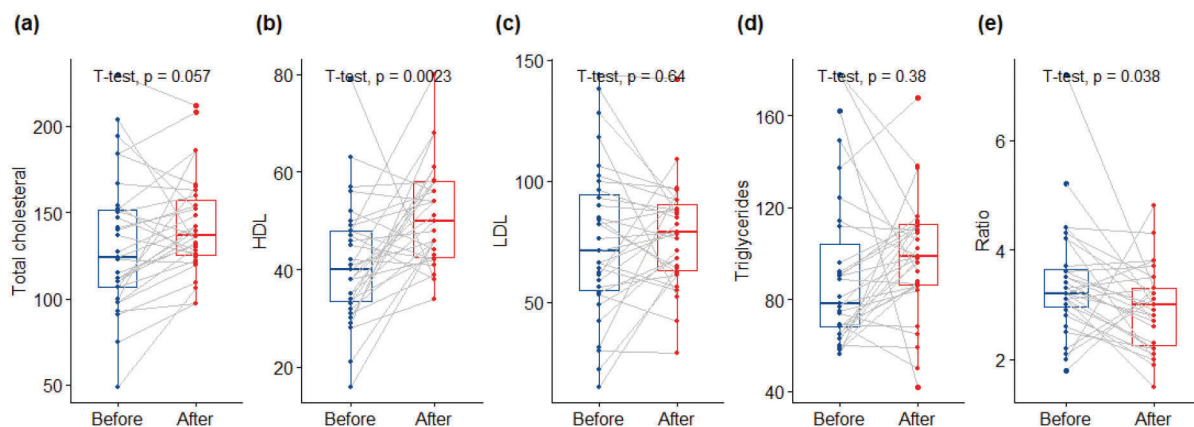


Figure-3: Change in lipid profile after six months of GFD.

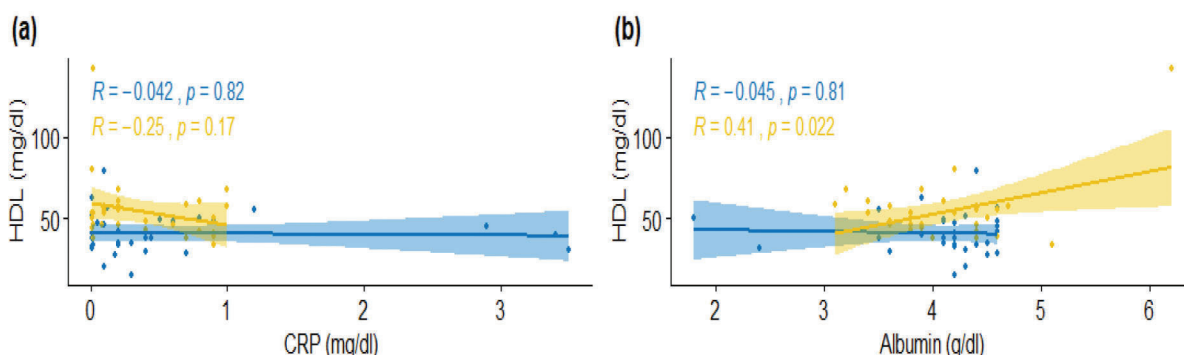


Figure-4: Correlation between HDL and CRP (a) serum albumin (b) before (shown in blue colour) and after 6 months (shown in orange colour) of gluten free diet.

Lipid profile	Before GFD (n=31)	After GFD (n=31)	Difference (95% CI)	P-value
TC				
Overall	131.8±39.7	142.7±28.5	10.8 (-0.36 to 22.1)	0.057
Male	135.6±34.3	146.3±26.7	10.7 (-7.4 to 28.8)	0.228
Female	126.5±47.2	137.6±31.3	11.1 (-2.0 to 24.1)	0.089
HDL				
Overall	41.2±12.6	54.2±19.3	13.0 (4.9 to 21.3)	0.002
Male	42.8±12.6	50.4±9.6	7.6 (-1.2 to 16.6)	0.087
Female	38.9±12.7	59.4±27.3	20 (5.0 to 35.9)	0.013
TC/ HDL Ratio				
Overall	3.4±1.0	2.9±0.7	-0.5 (-0.9 to -0.03)	0.037
Male	3.5± 2.9	3.0±0.9	-0.5 (-1.2 to 0.2)	0.125
Female	3.3±0.9	2.9±0.6	-0.4 (-0.9 to 0.2)	0.158
Triglyceride				
Overall	92.0±35.5	98.2±25.7	6.2 (-7.9 to 20.2)	0.376
Male	87.2±36.4	97.6±23.6	10.3 (-6.0 to 26.7)	0.200
Female	98.7±34.5	99.1±29.3	0.4 (-27.1 to 27.9)	0.975
LDL				
Overall	75 ± 32.3	77.4±21.5	2.4 (-7.8 to 12.6)	0.640
Male	77.1±31.7	83.6±21.1	6.4 (-4.7 to 17.7)	0.238
Female	72.1±34.2	68.7±19.8	-3.3 (-24.0 to 17.3)	0.732

Table-1: Mean lipid profile among celiac children (males and females) at the time of diagnosis and six months after GFD. TC-total cholesterol; LDL-low-density lipoprotein; HDL-high density lipoprotein*. All values are expressed as mean ±SD and measured in milligrams/decilitre.

Most common GI symptoms were diarrhoea (67.74%), pain abdomen (48.39%) and abdominal distension (38.71%). Among non GI presentation, poor weight gain (45.16%) and pallor (35.48%) were the predominant presentations.

At diagnosis 38.71% children were underweight, 51.61% of children had wasting, and 64.52% had stunting respectively (Fig.2). Diarrhoea (9.68%), vomiting (0) and pallor (0) reduced

significantly after 6 months of GFD. Clinically we observed weight gain after GFD but it was not statistically significant ($p < 0.068$). An improvement in BMI after 6 months of GFD was significant ($p < 0.036$). Two children (6.45%) were found to be overweight at diagnosis and at 6 months but none was obese.

Amongst different lipid parameters, only two parameter viz. HDL and TC/ HDL Ratio were found statistically different after GFD (Table 1).

On an average there was an increase of 13 mg/dl (95% CI: 4.9 to 21.3) in HDL after GFD compared to baseline (Fig.3). Further, average increase in HDL was higher in females {average increase (95% CI):20 (5.0 to 35.9)} than males (average increase {95% CI}: 7.6 (-1.2 to 16.6)}. TC/ HDL ratio was decreased significantly after GFD {average decrease (95% CI): -0.5 (-0.9 to -0.03)}.

Mean albumin level was normal at diagnosis and six months after GFD (4.07 +/- 0.6 g/dl and 4.1 +/- 0.6 g/dl; $p=0.429$). Median CRP level was also normal at diagnosis and after 6 months (P50 (P25 to P75): 0.2 (0.05-0) mg/dl; and 0.2 mg/dl; 0.02- 0.8). There was no correlation between HDL and albumin pre GFD. Slight positive change was observed after GFD, however it was not statistically significant (Fig.4).

DISCUSSION

Studies done from India have reported mean age at diagnosis around 8-9 years with mean duration of illness ranging between 2.9 – 5.9 years.^{19,20} Similarly, in our study children presented around 8 years with prior duration of illness ranging up to 96 months. This prolonged duration may be attributed to lack of awareness and diagnostic facilities for celiac disease in peripheral centres and high incidence of infectious diarrhoea in this part of the world.

Children on a strict GFD have faster and higher rates of symptom resolution as compared to adults.²¹⁻²³ Our study group also showed significant improvement in symptoms over six months. The percentage of children in underweight group decreased from 51.61% to 25.81% and 64.52% to 29.03% in the stunted category within 6 months of GFD. BMI improved significantly. Few studies in children have shown rising percentage of overweight celiac.²⁴⁻²⁶ However in our study only two children were overweight at diagnosis and at 6 months (6.45%). This could be due to geographic variation or referral bias in a gastroenterology clinic. Effect of GFD in this group is controversial. Cheng et al demonstrated 15.2% overweight and 6.8% obese in their study group before GFD and around 50% of them lost weight on GFD while in longitudinal studies adults patients who are normal or overweight at diagnosis have been shown to become overweight or obese after GFD.²⁷⁻²⁹ This needs to be correlated with GFD diet composition and lifestyle.

Different studies have shown variable results with respect to cholesterol levels in patients with celiac disease.^{8, 10,11,14,30} Celiac's have traditionally been associated with low plasma total cholesterol levels possibly due to fat malabsorption, reduced cholesterogenesis and high faecal elimination of cholesterol. Few studies have shown normal levels

attributable to subclinical diagnosis of celiac.¹⁰ HDL has also been found to be low among celiac due to decreased Apo-A1 secretion.^{31,32} However, in our study despite having predominantly gastrointestinal presentation and total villous atrophy at diagnosis, the mean total cholesterol level and mean HDL level was within normal range. This could possibly be explained by young age of our study population. Normal mean albumin levels despite complete villous atrophy at diagnosis support this explanation.

Men have been shown to have greater malabsorption and lower TC levels as compared to women among adult celiac.³³ We found girls had lower mean TC, LDL and HDL values at the time of diagnosis but difference was statistically insignificant.

HDL cholesterol is regarded as a potent anti-atherogenic mediator with anti-inflammatory, anti-oxidative and anti-thrombotic properties.³¹ Estimated coronary heart disease risk for each 1mg/dl increase in HDL-C is 2% in men and 3% in women.^{34, 35} The present study shows that HDL-C levels were significantly increased among the cases after 6 months of GFD ($p < 0.001$). We also found gender difference. Girls demonstrated a significant rise compared to boys. This could be due to maximum rise among those, with lowest levels at baseline as seen in other studies.¹⁴ Also, the ratio of total cholesterol to HDL-C was significantly reduced ($p < 0.02$).

Total cholesterol, serum triglycerides and LDL –C were also increased among the cases after 6 months of GFD but it was not statistically significant. This rise could be related to quantity and type of fat in the diets.^{36,37} The results support the hypothesis that even though GFD increases total cholesterol in our body, the healthy cholesterol that is HDL is the major component and thus Gluten free diet decreases the cardiovascular risk in celiacs.^{11,30,35} De Marchi et al observed that, GFD was associated with an increment in mean total cholesterol and HDL-C (68.2 ± 17.4 vs. 51.4 ± 18.6 mg/dL; $P < 0.001$) and a significant improvement in the total cholesterol/HDL-C ratio (3.05 ± 0.71 vs. 3.77 ± 0.92 ; $P < 0.02$) like in our study.⁴ Even up to 9% increase in HDL-cholesterol has been noted with treatment. Total cholesterol is mainly composed of LDL-C and HDL-C. Significant increase in HDL on GFD has been attributed to increased synthesis of Apo-A1 protein and down regulation of hepatic LDL receptors due to improved absorption of dietary fat.^{8,32,38,39}

Studies suggest that patients with elevated basal levels of CRP are at an increased risk of atherosclerosis and cardiovascular disease.⁴⁰ Previous study by De Marchi et al. showed that the levels of C-reactive protein was significantly decreases with GFD (1.073 ± 0.51 vs. 1.92 ± 1.38 mg/dL; $P < 0.05$).⁴ However, our study showed normal C-reactive protein levels in the cases before and after 6 months of GFD.

The limitations of our study is short follow up period and lack of analysis of GFD in terms of percentage of saturated fat and fibre content.

CONCLUSION

Our study found normal lipid profile in children with celiac

and beneficial effect of gluten-free diet on cardiovascular risk profile as a result of increase in HDL-C plasma concentration and lower TC/HDL ratios. The insignificant rise in triglycerides and LDL-C needs to be studied over longer duration of GFD to give us more insight.

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