Original Research Article

Dyslipidemia and Liver Function Profile in Children With Celiac Disease

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Abstract

Introduction: Different studies have shown variable results with respect to cholesterol levels in patients with celiac disease**.** The exact incidence of fatty liver or other forms of hepatic involvement is not known. Hence we decided to evaluate children with celiac disease.**Materials and methods:** 36 Children between the age group of 1-18 years with the diagnosis of celiac disease, Age and sex matched controls were enrolled. They were evaluated for liver dysfunction, dyslipidemia and presence of features of fatty liver on ultrasound evaluation.**Results:** Children with celiac disease had significantly elevated liver enzymes as compared to controls with mean values of AST and ALT being 59.47 ± 45.7 U and 41.19 ± 31.34 U as compared to 24.58 ± 10.19 U among the controls with a p value of 0.001. Total Serum Cholesterol, HDL-C and LDL-C levels were significantly decreased among the cases with mean values of 129.97 ± 39.29 mg/dl, 38.25 ± 12.88 mg/dl and 72.88 ± 31.26 mg/dl respectively (p value of 0.005, 0.002, and 0.040). Triglycerides were lower with a mean of 100 ± 47.04 mg/dl (p value 0.417) and the ratio of Total cholesterol to HDL-C was higher among the cases with a mean 3.59 ±1.01 but failed to show any statistically significant difference (p value 0.279). 8 (22.2%) children with celiac disease had features of fatty liver on USG compared to only 3 controls (8.3%) with a p value of 0.006.**Conclusion:**A significant number of celiac patients have co existing derangement in lipid profile, raised transaminases and also presence of fatty liver. Thus there is a need to regularly screen children with celiac disease for dyslipidemia, liver dysfunction and presence of fatty liver.

Key words: celiac disease, lipid profile, fatty liver, liver function.

Introduction

Celiac disease is a chronic small bowel enteropathy with an underlying autoimmune mechanism. Clinical spectrum of celiac diseaseincludes symptoms of frank malabsorption also many extra intestinal manifestations. Different studies have shown variable results with respect to cholesterol levels in patients with celiac disease. It is found to be most commonly associated with hypercholesterolemia with low levels of total, LDL-cholesterol and most importantly HDL-cholesterol. [1,2]

Lower cholesterol levels in the celiac patients can be explained by mechanisms based on intestinal malabsorption, reduced synthesis and increased elimination through bile.[3,4] Treatment with GFD leads to an increase in total cholesterol, however since the prominent effect is on HDL-cholesterol with a decrease in LDL/HDL ratio, it results in an improved lipoprotein profile. [5] Even up to 9% increase in HDL-cholesterol has been noted with treatment.[5] Significant decrease in HDL-cholesterol in comparison to LDL-cholesterol in patients with CD can be explained by the fact that intestine is the major source of both HDL and apo-A1, the main Apo protein of circulating HDL.[6] Apo-A1 protein synthesis is virtually absent in active celiac disease.[7]With treatment, there is increased absorption of dietary fat leading to down regulation of hepatic LDL-receptors and hence leading to increased HDL levels.[5]

Serum cholesterol level is a well-known risk factor for adverse cardiovascular events. While LDL-cholesterol has a critical importance in atherogenesis, HDL-cholesterol has a greater significance as a protective factor.[8] HDL cholesterol is regarded as a potent anti-atherogenic mediator with anti-inflammatory, anti-oxidative and anti-thrombotic properties.[9,10]With an

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inverse association with the proxy markers of vascular inflammation, HDL-cholesterol has also shown to have an attenuating effect on systemic inflammation, vessel wall inflammation and in turn ischemic heart disease events.[11,12] Thus it is very important to detect dyslipidemia right at the point of diagnosis of the disease for proper follow up.

Hepato-biliary manifestations in celiac disease include isolated raise liver enzymes, fatty liver, Autoimmune cholangitis, Autoimmune hepatitis, Primary biliary cirrhosis etc. The exact incidence of fatty liver or other forms of hepatic involvement is not known.The diagnostic standard of reference for fatty liver is biopsy with histologic analysis, but fat deposition in the liver may be diagnosed noninvasively with US, CT, or MR imaging if established criteria are applied. The most common imaging pattern is diffuse and relatively homogeneous fat deposition. Less common patterns include focal deposition, diffuse deposition with focal sparing, multifocal deposition, perivascular deposition, and sub capsular deposition. In this study, we decided to evaluate children with celiac disease for presence of dyslipidemia, fatty liver and evaluate liver function profile at the time of diagnosis.

Materials and methods

Thirty six children between the age group of 1-18 years with the diagnosis of celiac disease (newly diagnosed) were enrolled for the study group. Thirty sixAge and sex matched children coming for routine vaccinations, minor afebrile illnesses and healthy siblings of the cases were enrolled for the control group. Children with known chronic liver diseases and those on drugs affecting serum lipid levels (statins, steroids etc.) or conditions with hyperlipidemia like nephrotic syndrome, congenital hyperlipidemias, Cushing's disease, and hypothyroidism were excluded from the study. Informed written consent was taken from all the participants before the enrollment.

For the purpose of study

Celiac disease was defined based on the guidelines by World Gastroenterology Organization -Guidelines for Celiac Disease2012 for Children.[13]Children with clinical symptoms **OR** asymptomatic children with family history **With** positive serology* (IgA anti tTG antibodies)**And** biopsy findings (evidence of villous atrophy– Marsh staging 3)

After enrollment, Venous blood from a peripheral vein was drawn after an overnight fasting and samples were collected in appropriate collection vials. Serum was analyzed for Liver Function test by Calorimetric methods.Serum fasting Lipid profile:

i. Total serum cholesterol and serum triglycerides levels were measured using cholesterol oxidase and colorimetric methods.
ii. HDL cholesterol levels were measured by direct non-immunological assay.
iii. LDL cholesterol levels were calculated by Friedwald (1972) formula [LDL = TC - HDL - TG/5.0 (mg/dL)].

The laboratory values were assessed according to standard reference valuesfor age and sex. [14]
Enrolled children were studied under standardized conditions, in a quiet room at a comfortable temperature. The ultrasonography was done using High Resolution B-mode ultrasonography with a 7.5 MHz linear array transducer by a single experienced radiologist, blinded to the participant's case status and risk factors.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before 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 all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results

Among the 36 cases included, youngest was 3 years old while the oldest was 16years with a mean age of 7.72 ± 3.26 years. The control population was comparable in age distribution with a mean of 7.56 ± 3.18 years.Majority of the cases were <5years of age constituting 36.1%. The cases as well as controls had similar distribution with 44.4% females and 55.6% male subjects. Majority (50.0%) of the cases had been symptomatic for 6-24 months before diagnosis with a mean duration being 22.47 ± 20.47 months.

Table1: Parameters among cases and controls

Parameter	Cases	Controls	P value
	Mean ± SD	Mean ± SD	
AGE (Years)	7.72 ± 3.26	7.56 ± 3.18	0.827
Total Bilirubin (mg/dl)	0.56 ± 0.24	0.61 ± 0.16	0.093
Direct Bil(mg/dl)	0.2 ± 0.1	0.2 ± 0.08	0.554
IndirectBil(mg/dl)	0.36 ± 0.18	0.41 ± 0.12	0.017
AST (U/L)	59.47 ± 45.7	32.42 ± 11.45	<0.001
ALT (U/L)	41.19 ± 31.34	24.58 ± 10.19	0.001
ALP (U/L)	233.14 ± 88.97	232.78 ± 133.58	0.528
S Total Protein (g/dl)	7.15 ± 0.84	7.04 ± 0.63	0.313
Albumin(g/dl)	4.05 ± 0.59	3.83 ± 0.64	0.080
Albumin/Globulin ratio	1.34 ± 0.3	1.23 ± 0.29	0.100
Total Cholesterol (mg/dl)	129.97 ± 39.29	150.47 ± 28.1	0.005
HDL- Cholesterol (mg/dl)	38.25 ± 12.88	46.69 ± 11.6	0.002
LDL- Cholesterol (mg/dl)	72.88 ± 31.26	89.19 ± 31.869	0.040
Triglycerides (mg/dl)	100 ± 47.04	104.56 ± 37.864	0.417
T Chol/HDL- Chol ratio	3.59 ± 1.01	3.32 ± 0.87	0.279
Fatty liver on USG: number (%)	8 (22.2%)	3 (8.3%)	0.006

As shown in table 1, Serum bilirubin and serum protein levels were normal among the cases and controls. Whereas liver enzymes viz. alanine transaminase and aspartate transaminase were significantly raised in cases as compared to controls (p value <0.001 and 0.001 respectively). Lipid profile revealed significantly lower mean serum levels of Total cholesterol, HDL-cholesterol as well as LDL- cholesterol in cases (p value of 0.005, 0.002 and 0.040 respectively). Mean serum Triglycerides levels were low in cases though not statistically significant (p value 0.417). Although the Total cholesterol to HDL-cholesterol ratios were increased among the cases, it was also found to be not statistically significant (p value 0.279).

Discussion

Children with celiac disease had significantly elevated liver enzymes as compared to controls with mean values of AST and ALT being 59.47 ± 45.7 U and 41.19 ± 31.34 U as compared to 24.58 ± 10.19 U among the controls with a p value of 0.001. No such elevation of bilirubin levels was noted and none of the patients were clinically jaundiced.Studies done in the past have demonstrated similar results with Novacek et al.[15] in 1999 showing 40.4% prevalence of raised liver enzymes, Bardella et al.[16] in 1995 and Castillo et al. in 2015 showing 42% and 40.6% of the celiac patients to have raised liver enzymes. Such asymptomatic or subclinical elevation of transaminases can be attributed to the disease process itself though it is recommended that their persistent elevation even

after successful treatment with GFD needs further evaluation into the cause as celiac disease is also known to be associated with liver disorders like autoimmune hepatitis etc.[17]

Total Serum Cholesterol, HDL-C and LDL-C levels were significantly decreased among the cases with mean values of 129.97 ± 39.29 mg/dl, 38.25 ± 12.88 mg/dl and 72.88 ± 31.26 mg/dl respectively (p value of 0.005, 0.002, and 0.040). Triglycerides were lower with a mean of 100 ± 47.04 mg/dl (p value 0.417) and the ratio of Total cholesterol to HDL-C was higher among the cases with a mean 3.59 ±1.01 but failed to show any statistically significant difference (p value 0.279). Thus, the changes observed in lipid profile of the celiac patients might be detrimental despite decrease in absolute levels due to altered proportions of HDL and LDL cholesterol. [9, 10]

Pitocco et al. [18] in their study demonstrated lower values of Total and HDL-cholesterol and higher values of Triglycerides and LDL-C as compared to control population, although not statistically significant. De Marchi et al. [19] observed significantly lower levels of Total, LDL, HDL-C and triglycerides like in our study. While the above two studies included young adult patients, the results of study by Demir et al. [20] including children from 6-18 years were not significant statistically.

The echogenicity of the normal liver equals or minimally exceeds that of the renal cortex or spleen. Fatty liver may be diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture [21]. To avoid false-positive interpretations, fatty liver should not be considered present if only one or two of these criteria are fulfilled.Reported sensitivities and specificities for detection of fatty liver deposition are 60%–100% and 77%–95% for US [21].

In our study, 8 (22.2%) children with celiac disease had features of fatty liver on USG compared to only 3 controls (8.3%) with a p value of 0.006. among them 6 had increased liver echogenicity and 2 had poor delineation of intrahepatic structure. In a Population-based cohort study by Reilly NR et al. [22], it was found that Individuals with celiac disease are at increased risk of nonalcoholic fatty liver disease compared to the general population. Excess risks were highest in the first year after celiac disease diagnosis, but persisted through 15 years beyond diagnosis with celiac disease. In another prospective longitudinal study by Kamal S et al. [23], patients with NAFLD were screened for Celiac Disease and Celiac Disease was confirmed in 7.2% of patients with NAFLD. Thus there is a need to regularly screen children with celiac disease for dyslipidemia, liver dysfunction and presence of fatty liver.

Conclusion

A significant number of celiac patients have co existing derangement in lipid profile, raised transaminases and also presence of fatty liver. Thus there is a need to regularly screen children with celiac disease for dyslipidemia, liver dysfunction and presence of fatty liver.

Limitations

Follow up assessment after treatment was not done. An US imaging–based diagnosis of fatty liver may be unreliable in the presence of a liver fat content of less than 30% in wet weight

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