The association between liver function changes and celiac disease in children

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Abstract

Background: Celiac Disease (CD) is known as a gluten enteropathy, it is a disease that affects many organs, and findings outside the gastrointestinal tract are common. CD-associated liver disease is probably developed by variable factors, comprising intestinal bacterial overgrowth, chronic infection and inflammation, gut permeability, genetic, molecular mimicry, and predisposition of genes.

Objectives: Assessment of liver function in patients with celiac Disease.

Patients and Methods: A cross-sectional study was conducted, included 62 newly diagnosed children with celiac disease, at Pediatrics Hepatology Department - Children Welfare Teaching Hospital during period from 1st February 2023 till 1st November 2023. Data was collected using a questionnaire paper including personal and clinical examination with baseline requested lab investigations. Data including 62 child with newly diagnose celiac disease approved by positive serology and endoscopic findings. The questionnaire includes demographic and anthropometric measurements, initial presentation and laboratory investigations (complete blood count, blood film, liver function tests) Data frequencies and percentages were represented by tables and figures. P value < 0.05 was considered as statistically significant.

Results: Mean age of participants was 7.7±1.9 years, and mean BMI of 15.24±2.19 kg/m2. Males were 28 (45.2%) while females were 34 (54.8%). A significant higher Body mass index of females in comparison to males was found (P<0.001). According to the first presentation, there were 19 (30.60%) participants presented to screen for celiac disease because of short stature, 17 (27.40%) with diarrhea, 6 (9.70%) with anemia, 4 (6.50%) with abdominal pain. Marsh score was 1 among 18 (29.0%) participants, score 2 among 15 (24.2%), and score 3 among 29 (46.8%). Mean level of ALT was 49.06±26.77 (IU/l), mean of AST was 41.79±32.22 (IU/l), and mean of TSB was 0.59±0.27 μmol/l.

MARSH score 3 was associated significantly with weight and height at ≤5th percentile, underweight, short stature, with lower BMI mean, and with higher

levels of anti-tissue IgA, anti-tissue IgG, ALT, and AST; (P<0.05). Higher ALT and AST levels were associated significantly with short stature (P=0.001). There was a significant decrease in the mean level of both ALT and AST after 3-6 months gluten-free diet (GFD) introduction in comparison to those before GFD; P<0.001.

Conclusions: Nearly half (46.8%) of participants presented as Marsh score 3. MARSH score 3 was dominant among participants with short stature, lower Body mass index , and with higher levels of anti-tissue IgA, anti-tissue IgG, Higher levels of liver enzymes (ALT and AST) were associated significantly with short stature. There was a significant decrease in the mean level of liver enzymes after 3-6 months gluten-free diet.

INTRODUCTION

Celiac disease (CD) is a disease that predominantly affects the proximal small intestine and is characterized by persistent intolerance to the gluten in wheat and other gluten-like grain proteins found in grains such as barley, rye, and oats. Although CD is known as an enteropathy, it is a disease that affects many organs, and findings outside the gastrointestinal tract are common [(1)] .

CD is a systemic disease, as the clinical manifestations are not limited to the intestinal tract: indeed, it is estimated that a significant portion of CD cases are currently undiagnosed, and its great clinical heterogeneity with 'atypical' and variable extra-intestinal manifestations is undoubtedly a major contributing factor [(2)].

One of the extra-intestinal features of CD is hepatic dysfunction, which ranges from asymptomatic liver enzyme elevations or non-specific hepatitis to chronic liver disease. The majority of studies determine the percentage of patients with hypertransaminasemia or the association between CD and liver diseases, but they do not estimate other pathological hepatic changes [(3)].

CD-associated liver disease is probably developed by variable factors, comprising intestinal bacterial overgrowth, chronic infection and inflammation, gut permeability, genetic, molecular mimicry, and predisposition of genes [(4)]

Aim of the study

Assessment of liver function in pediatric patients with newly diagnose celiac disease and follow up of liver function after 3-6 months with gluten free diet .

PATIENTS AND METHODS

A cross sectional study was carried out at Children Welfare Teaching Hospital - Medical City Complex in Baghdad; Iraq , from 1st February 2023 till 1 st November 2023.

Newly diagnosed children with celiac disease, who attended out-patients clinic. A convenience sampling was carried out from children younger than 15 years old of both sexes, and newly diagnosed with celiac disease (by serology and intestinal biopsy).

Data was collected through direct interviews with children and their parents in the GIT outpatients' clinic in the hospital; using a structured questionnaire that was prepared by the researcher. Data was collected for nine consecutive months/ 3 days per week. All children were subjected to the following: Full history taking, clinical examination, laboratory investigations, and endoscopy.

The questionnaire includes demographic data and anthropometric measurements, Initial presentation, time of diagnose, method of diagnosis, type of feeding, laboratory investigations (CBC, LFT, IgA assay, Anti-tissue transglutaminase Ab), Small intestinal biopsy results, follow up findings after 3- 6 months by doing liver function tests while they were on gluten free diet.

Statistical analysis:

Microsoft Excel 2010 and IBM SPSS version 26 were used for data entry, management, and analysis. Descriptive analyses of the variables were expressed as frequencies and percentage for categorical data. While mean of standard deviation was used for quantitative data that is normally distributed, represented by figures and tables. To compare qualitative variables, we utilized the chi-square test, and we used $P< 0.05$ to determine statistical significance.

RESULTS

A total of 62 patients were included in the study with a mean age of age 7.7±1.9 years, and mean BMI of 15.24±2.19 kg/m2. No significant difference between gender and mean age (P=0.22).

There were 30 (48.4%) participants aged less than 8 years and 32 (51.6%) participants aged 8 years or more, 28 participants (45.2%) were males, and 34 (54.8%) participants were females. Participants with healthy weight were 43 (69.4%); those with underweight were 19 (30.6%). Marsh score was 1 among 18 (29.0%) participants, score 2 among 15 (24.2%), and score 3 among 29 (46.8%). As shown in table 1.

Table 1: Demographic data of the studied sample

Demographic data		Number	Percentage
Age/ years	<8	30	48.4%
	≥8	32	51.6%
Gender	Male	28	45.2%
	Female	34	54.8%
BMI Categories	Underweight (<5th percentile)	19	30.6%
	Healthy weight (5th-95th percentile)	43	69.4%
Anemia	present	7	11.3%
	absent	55	88.7%
Marsh score	1	18	29.0%
	2	15	24.2%
	3	29	46.8%
Total	62		100.0%

Males were 28 (45.2%) while females were 34 (54.8%). A significant higher BMI of females in comparison to males was found (P<0.001). **Table 2**.

Table 2: Mean age and BMI according to the gender of the studied sample

	Gender				P- value
	Male		Female		
	Mean	SD	Mean	SD	
Age/ months	88	26	91	19	0.22
BMI	14.07	1.81	16.20	2.01	<0.001
Total no.(%)	28	45.2%	34	54.8%	

Abdominal distention was found among 26 (41.9%), Screen for celiac because of short stature was found among 19 (30.6%), diarrhea among 17 (27.4%), anemia

among 7 (11.3%), abdominal pain among 4 (6.5%), and constipation among 3 (4.8%). **Table 3.**

Table 3: Clinical symptoms and signs of the studied sample

Clinical symptoms	Number	Percentage
Abdominal distention	26	41.9%
Screen for celiac because of short stature	19	30.6%
Diarrhea	17	27.4%
Pallor	7	11.3%
Abdominal pain	4	6.5%
Constipation	3	4.8%

MARSH score 3 was associated significantly with lower BMI mean, and with higher levels of Anti-tissue IgA, Anti-tissue IgG, ALT, and AST; ($P<0.05$). **Table 4**.

Table 4: Mean distribution of laboratory data of the studied sample according to the MARSH score

Variables	MARSH						P-value
	MARSH 1		MARSH 2		MARSH 3		
	Mean	SD	Mean	SD	Mean	SD	
Age/years	7.4	2.1	7.2	1.1	8.1	1.9	0.22
Anti-tissue IgA/IU	31.14	45.14	38.40	20.64	122.76	67.94	<0.001
Anti-tissue IgG/IU	27.92	44.13	44.35	28.00	116.93	70.29	<0.001
ALT (IU/l)	31.94	12.27	35.73	16.87	66.59	26.95	<0.001
AST (IU/l)	22.94	10.50	27.80	19.86	60.72	35.96	<0.001

TSB m.mol/l	0.63	0.27	0.53	0.23	0.60	0.30	0.60
Hb g/dl	11.18	2.40	10.90	2.05	10.06	1.63	0.13
WBC*10^9/L	7.02	5.77	7.99	3.53	9.40	3.34	0.16
PLATLETS	253.33	60.05	299.87	76.81	284.83	119.43	0.35

There was a significant decrease in the mean level of both ALT and AST after 3-6 months gluten-free diet (GFD) introduction in comparison to those before GFD; P<0.001. **Table 5.**

Table 5: Changes of mean values of liver function (ALT, AST) parameters before and after 3 months gluten-free diet (GFD) introduction

Variables		**Mean**	**SD**	**P* value**
ALT (IU/l)	Before	49.0645	26.77096	<0.001
	After	21.1935	4.42733	
AST (IU/l)	Before	41.7903	32.22215	<0.001
	After	30.5806	12.04710	

DISCUSSION

In the current study, a total of 62 patients were selected, and their mean age was (7.7±1.9) years. More than half of the recruited samples were females. Those findings agreed with other studies, the first one was conducted by Şeker et al.,[(5)] in Turkey (2022), where the mean age and the standard deviation of patients were (7.1±4.3) years, and (64%) of their sample were females. The second study was by Sukkar et al.,[(6)] 2020 who found that the mean age was (7.71±3.09). The third one was done by Shahraki et al.,[(7)] 2018 where the mean ± standard deviation of the age of the selected sample was (7.4±3.8) and (62%) of the patients were females. The current data, however, provide credence to the theories that gender biology plays a part in the development of the illness. The pathophysiology behind the greater occurrence of CD in females is yet unknown. This theory is supported by genetic variables, including permissive HLA, X chromosomal gene variants, and a greater prevalence in female relatives of CD patients [(8-10)].

The mean and the standard deviation of BMI were (15.24±2.19) kg/m2, which was in accordance with Sukkar et al.,[6] 2020 and Dehghani et al.,[11] 2017 who stated that the mean BMI of their patients was (15.44±3.65) and (15.62±3.47) respectively. A significantly higher BMI of females in comparison to males was found (P<0.001). This was inconsistent with Dehbozorgi et al.,[12] 2020 who demonstrated that there was no statistically significant difference in BMI between girls and boys within the celiac disease group (p = 0.51). This difference may be explained by the differing inclusion criteria regarding age groups, where our study included those younger than 15 years old, while the other study included children younger than 18 years old, which might affect the BMI of boys and girls. It was observed that more than one-half of the participants were of healthy weight, and the underweight ones made up less than one-third. This was similar to the results of the study by Dehghani et al.,[11] 2017 where (63.6%) were with normal weight and (27%) were underweight.

Abdominal distention was the most common clinical symptom found among less than one-half of the recruited children, followed by screening for celiac disease for short stature, which was found among less than one-third. That went in the same trend as other studies, one of them was done by Saadah et al.,[13] 2021 where abdominal distension was demonstrated among (36%) of their patients. And the other study was conducted by Kochhar et al.,[14] 2012 where (45%) of children had abdominal distension.

Regarding the other findings of the selected sample, less than one-third had short stature, and the minority had diabetes mellitus or had a family history of celiac disease. Those findings were consistent with what was observed by Tolone et al.,[15] 2021 who reported that (20.6%) of their sample had short stature, and (19%) were with a family history of celiac disease. Also, Halabi et al.,[16] 2023 similarly found that type 1 diabetes mellitus was observed among (11%), and (18%) had a first-degree relative with celiac disease.

Less than one-half of the patients in the current study had a Marsh score of 3, and the remaining scored 1 or 2, which was in agreement with Isa et al.,[17] 2021 who observed that Marsh-Oberhuber type III was found among (45.7%) of their patients. But our findings were lower than what was stated by Saadah et al.,[13] 2021 where (97%) of patients were determined to have a severe form of CD (Marsh score 3). This difference might be because the participants of the study by

Saadah et al. were older than the participants of this study and it is more common to observe advanced histopathological stages in older children [18].

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS:

1. As a first presentation, 30.60% of participants presented to screen for celiac because of short stature and 27.40% with diarrhea.
2. Nearly half (46.8%) of participants presented with Marsh score 3.
3. MARSH score 3 was dominant among participants with weight and height at ≤5th percentile, underweight, short stature, lower BMI, and with higher levels of Anti-tissue IgA, Anti-tissue IgG, ALT, and AST.
4. Higher ALT and AST levels were associated significantly with short stature.
5. There was a significant decrease in the mean level of both ALT and AST after 3-6 months gluten-free diet.

RECOMMENDATIONS:

Further studies should be implemented with larger sample size and longer duration to clarify the effect of celiac disease and gluten free diet on liver enzymes and longer duration for follow up of liver enzymes.

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