

## The Effects of Gluten-Free Diet on Hypertransaminasemia in Patients with Celiac Disease

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### ABSTRACT

**Background:** Celiac disease (CD) is an immune mediated condition that leads to small bowel atrophy that resolves with a gluten free diet (GFD). Extra-intestinal manifestations of CD include hypertransaminasemia. In this study, the effects of a GFD on hypertransaminasemia in patients with newly diagnosed CD were studied.

**Methods:** Ninety eight new diagnosed consecutive patients with CD (40 males and 58 females) with mean age of  $32 \pm 17.1$  were studied. All patients with CD were treated with a GFD. Patients with hypertransaminasemia, at diagnosis, had a cirrhosis screen performed. Patients with a negative cirrhosis screen were reviewed, 6 months after the introduction of a GFD, and serum levels of liver transaminases were measured again.

**Results:** Nine patients had hypertransaminasemia. One patient was Hepatitis B surface antigen positive and was excluded from this study. The 8 remaining patients had no obvious cause for the hypertransaminasemia. Mean ( $\pm$  SD) of baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were  $42.6 \pm 16.5$  IU/L (range: 16-66 IU/L) and  $69.3 \pm 9.3$  IU/L (range: 52-81 IU/L). Six months after treatment with a GFD, mean AST and ALT levels decreased to  $24.5 \pm 5.1$  IU/L (range: 18-31 IU/L) ( $P$ : 0.04) and  $24.6 \pm 6$  IU/L (range: 17-32 IU/L) ( $P$ : 0.01), respectively. In 7 patients the hypertransaminasemia, at diagnosis had resolved.

**Conclusions:** This study provides further evidence that some patients with CD have a reversible hypertransaminasemia that resolves with a GFD.

**Keywords:** Celiac disease, gluten-free diet, hypertransaminasemia, liver

### INTRODUCTION

Celiac disease (CD) is an immune-mediated disease, leading to small bowel atrophy that resolves upon the introduction of a gluten free diet (GFD). Symptoms can include steatorrhea, weight loss, and fatigue. CD can also be asymptomatic. CD

affects approximately 1% of the Iranian general population.<sup>[1,2]</sup> CD can affect extraintestinal organs, such as the skin, pancreas, heart, and liver.<sup>[3]</sup> Previous studies have suggested that up to 9% of patients with hypertransaminasaemia and negative investigations to identify chronic liver disease, have CD.<sup>[4]</sup> Studies have reported that patients with CD have an increased incidence of auto-immune and cryptogenic liver disease compared to the general population.<sup>[5,6]</sup> The cryptogenic liver disorder associated with CD is characterized by hypertransaminasemia with non-specific histological changes.<sup>[7]</sup>

The mainstay of treatment of CD is adherence to GFD.<sup>[2]</sup> Mild liver dysfunction often improves with introduction of a GFD. Kaukinen, *et al.* showed that GFD may inhibit progression to hepatic failure, even in cases being considered for liver transplantation.<sup>[8]</sup> There is a little information on the association between liver disorders and CD in Iran. The only published study by Emami *et al.* on Iranian patients in Isfahan showed that serological screening for CD should be routinely performed in patients with abnormal liver function test (LFT). Moreover, they found effects of GFD in the improvement of abnormal LFT.<sup>[9]</sup> Designing similar study in order to evaluate the prevalence of liver dysfunction in patients with newly diagnosed CD patients and the effects of a GFD may more clarify the patients' problem and its solution. Therefore, the aim of this study was to evaluate the prevalence of liver dysfunction in patients with newly diagnosed CD patients and also the effects of a GFD were studied.

## METHODS

### Patients and settings

Newly diagnosed patients with CD, referred to Taleghani Hospital, Tehran, Iran, between September 2007 and September 2011 were recruited. The diagnosis of CD was based on duodenal biopsies with histological abnormalities characteristic of CD (the presence of any of the following: Intraepithelial lymphocytes, crypts hyperplasia and villous atrophy) and serology consistent with a diagnosis of CD (positive Immunoglobulin A (IgA) class human anti-tissue transglutaminase antibody, endomysial antibody and total serum IgA [If IgA deficient and IgG class human anti-tissue transglutaminase antibody (tTGG) was positive]).<sup>[10,11]</sup>

### Assessments

LFTs, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), were measured in all the patients. The serum levels of bilirubin (normal range: 0.2-1.3), AST (normal range: 15-35 IU/L), ALT (normal range: 11-35 IU/L) and ALP (normal range: 64-306 for adults and 180-1200 for children) were measured by routine laboratory methods. Patients with hypertransaminasemia had a cirrhosis screen performed to investigate possible causes of liver dysfunction. Hypertransaminasemia was defined by an increase in AST and (or) ALT > 2N.<sup>[12]</sup> The cirrhosis screen consisted of measuring serological markers for viral hepatitis, metabolic liver diseases and serum protein electrophoresis. Serologic markers for viral hepatitis, including Hepatitis B surface antigen (HBsAg) and Hepatitis C virus antibody were determined with commercially available (ELISA) Enzyme-linked immunosorbent assay kits (Dia Pro) Diagnostic Bioprobes (it is mentioned in the parenthesis, Diagnostic Bioprobes, Srl., Italy). Serum levels of Ferritin, TSH (Sigma/Aldrich, USA), caeruloplasmin, copper, ANA (anti-nuclear antibody), anti-smooth muscle antibody, anti-mitochondrial antibody and alpha-fetoprotein (DIA PRO Diagnostic Bioprobes, Srl., Italy) were evaluated. History of taking medications, using alcohol, exposure to hepatic toxins and co-morbidities, such as diabetes mellitus, were considered. Body mass index was calculated in patients to detect overweight or obese patients. Ultrasonography of hepato-biliary system was done. Levels of AST and ALT higher than 35 IU/L, increased serum bilirubin greater than 2 mg/dL and/or elevated serum ALP above 306 IU/L for adults and 1200 for children were considered as evidence of liver dysfunction. In patients with abnormal ALP values, serum levels of calcium and phosphate were determined. Patients with a specific diagnosis that might be responsible for altering LFT were excluded. Liver biopsy was performed in those patients with hypertransaminasemia and a negative cirrhosis screen.

All CD patients were treated with a GFD. Patients with undiagnosed causes of abnormal LFT were reviewed after 6 months and serum levels of AST, ALT, bilirubin and ALP were re-checked. We have asked all patients about continuing GFD each month.

The patients were assured that their private

information would be kept confidential and a written informed consent was obtained from them. The study was approved by the Ethics Committee of the Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences.

### Statistical analysis

Data were analyzed by SPSS software ver. 16 (Chicago, USA). Wilcoxon signed-ranks test used to compare mean before and after treatment.  $P < 0.05$  was considered significant.

## RESULTS

Ninety eight patients with confirmed CD (40 Males and 58 females) with mean age of  $32 \pm 17.1$  were studied. Nine patients had hypertransaminasemia. One patient with HBsAg was excluded in this survey and referred to gastroenterologist for further evaluation. Therefore, 8 patients (5 females and 3 males) with mean age of  $26.4 \pm 4.8$  years (range: 19-33 years) were studied and maintained GFD. Marsh II was reported in 2 patients, Marsh IIIa in three, Marsh IIIb in two and Marsh IIIc in one. None of the patients with abnormal LFT had deficiency in total IgA serum. There was no medical history of significant co-morbidities, excess alcohol consumption or exposure to known hepatotoxic agents. None of the patients were overweight or morbidly obese. Ultrasonographic evaluation of these 8 patients had no specific findings. Liver biopsy was unremarkable. None of the biopsies showed evidence of steatohepatitis.

At the beginning of the study, all 8 (8.1%) CD patients with undiagnosed liver dysfunction had normal bilirubin levels with mean value of  $0.95 \pm 0.2$  mg/dL (range: 0.7-1.3 mg/dL). Eight patients had abnormal ALT level and 5 of these 8 patients had abnormal AST. Furthermore, ALP levels were abnormal in 2/8 patients. Mean ( $\pm$ SD) AST and ALT levels were  $42.6 \pm 16.5$  IU/L (range: 16-66 IU/L) and  $69.3 \pm 9.3$  IU/L (range: 52-81 IU/L). Mean ( $\pm$ SD) concentration of ALP was  $240.3 \pm 118.7$  IU/L (range: 108-428 IU/L). Two of 8 patients with elevated levels of ALP had low levels of calcium, representing metabolic disorder.

Six months after using GFD, mean AST and ALT levels decreased to  $24.5 \pm 5.1$  IU/L (range: 18-31) ( $P: 0.04$ ) and  $24.6 \pm 6$  IU/L (range: 17-32 IU/L) ( $P: 0.01$ ), respectively. Billirubin levels decreased to  $0.9 \pm 0.2$  mg/dL (range: 0.7-1.1 mg/dL), although, not statistically significant differences were found ( $P: 0.33$ ). Concentration of ALP reduced to  $180.3 \pm 50.6$  IU/L (range: 108-260 IU/L) 6 months after using GFD and the differences with ALP values before GFD was not statistically significant ( $P: 0.09$ ). Except for 1 case with persistent abnormal LFT's, the rest of 7 cases LFT's have normalized after 6 month of GFD. The prevalence of reactive hepatitis in this cohort was 8% with almost complete resolution following GFD. Table 1 represents the serum levels of bilirubin, AST, ALT and ALP before and after following GFD.

## DISCUSSION

The pathogenesis of hypertransaminasemia in

**Table 1:** Liver function test results among celiac patients with hypertransaminasemia of no other cause, before and 6 months after gluten free diet

Patients	Age	Sex	Total bilirubin (mg/dL)		AST (IU/L) normal		ALT (IU/L) normal		ALP (IU/L) normal	
			normal range: 0.2-1.3	normal range: 0.2-1.3	range: 15-35 IU/L	range: 15-35 IU/L	range: 11-35 IU/L	range: 11-35 IU/L	range: 64-306	range: 64-306
			Before GFD	6 months after GFD	Before GFD	6 months after GFD	Before GFD	6 months after GFD	Before GFD	6 months after GFD
1	21	Male	0.8	0.7	66	24	81	31	243	218
2	19	Female	1.1	0.9	31	22	76	24	145	164
3	24	Female	0.7	0.7	48	30	63	27	428	216
4	29	Male	0.9	1	52	31	72	19	255	260
5	33	Female	1	0.8	16	24	65	17	108	124
6	27	Female	1.3	1.1	46	18	77	32	398	166
7	27	Male	0.7	0.9	27	29	52	29	137	108
8	31	Female	1.1	1.1	55	18	68	18	208	186

AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ALP=Alkaline phosphatase, GFD=Gluten free diet

CD is unidentified and several mechanisms have been proposed. We are aware of a link between CD and autoimmune disorder like autoimmune hepatitis, sclerosing cholangitis and primary biliary cirrhosis. However, most CD patients with elevated serum transaminases have no evidence of autoimmune disorder.<sup>[13]</sup> It has been suggested that the hypertransaminasemia in CD patients may be multifactorial and a complication of prolonged existence of malabsorption, small intestinal bacterial overgrowth, iron overload disorder, hepatic steatosis, chronic intestinal inflammation and enhanced absorption of toxic substances.<sup>[6,13,14]</sup>

In this study, 8% of adult CD patients had cryptogenic liver disorder and we did not find any evidence of autoimmune liver diseases. In a comparable study, Dicky, *et al.* reported a hypertransaminasemia in 15% of patients with newly diagnosed CD.<sup>[15]</sup> In previous studies, the frequency of elevated transaminases in patients with CD was 36-55%.<sup>[7,16,17]</sup> Possible explanations for this high prevalence of a hypertransaminasemia in other studies may include the very different populations studied. European patients may be more likely to consume excess alcohol and have a greater prevalence of non-alcoholic steatohepatitis than Iranian population.

Several studies showed that CD is commonly associated with autoimmune liver diseases. Di Biase, *et al.* evaluated a large population of children with CD in a prospective study. They found that hypertransaminasemia is presents in 40% of CD patients and autoimmune liver hepatitis is present in 2% of cases, while no other autoimmune liver diseases were found.<sup>[18]</sup> Caprai *et al.* assessed the association between an autoimmune liver disease and CD in a retrospective multicenter national survey between 1990 and 2005 in Italy. Of 140 patients with autoimmune liver disease, they determined 23 with CD. Patients underwent gluten-free diet and remission was observed in all of them. Fourteen patients relapsed after discontinuation of therapy or during spontaneous gluten challenge.<sup>[19]</sup>

It has been reported that hypertransaminasemia might be an initial presentation of CD.<sup>[20]</sup> Assessment of hypertransaminasemia in some studies has led to a diagnosis of CD in 10% of patients, using serological methods.<sup>[16,21]</sup> In Bardella *et al.* study, 13 out of 140 patients with elevated

transaminases were seropositive for gliadin and endomysial antibodies.<sup>[16]</sup> In a similar study, Volta *et al.* reported that in 55 patients with unexplained hypertransaminasemia, 5 had CD. In a similar study, Abdo *et al.* reported that CD serology was positive in 9% of patients with unexplained hypertransaminasemia.<sup>[4]</sup> We believe these studies suggest that clinicians should consider CD in the evaluation of patients with hypertransaminasemia.<sup>[19]</sup> In our study, 2 of the patients with newly diagnosed CD patients had elevated ALP values, a result comparable to the Bardella *et al.*, study.<sup>[16]</sup> This was secondary to hypocalcaemia induced by chronic malabsorption.

## CONCLUSION

Our study suggests that the hypertransaminasemia associated with CD resolves with the introduction of a GFD. This is in keeping with other studies that have reported an improvement in effects in the hypertransaminasemia associated with CD provided there was no evidence of underlying autoimmune, metabolic or viral liver disease.<sup>[8,16,18,20,22]</sup> This study showed that CD may be associated with hypertransaminasemia in the absence of other possible causes of liver dysfunction and clinicians need to consider the diagnosis of CD, when patients present with hypertransaminasemia. Furthermore, introduction of a GFD can improve the hypertransaminasemia and normalize the liver enzyme abnormality.

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