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Original Research Article

# Biochemical and Clinical Liver Abnormalities in Celiac Disease among Children and the Impact of Gluten Free Diet

**Dr. Pushwider Kaur[1], Dr Pushpendra magon[2]**
[1]Assistant Professor, [2]Professor
Department of Pediatrics, Punjab Institute of Medical Sciences, Garha Road, Jalandhar, Punjab, India

***Corresponding author**
Dr. Pushwider Kaur
Email: pushwinder566@gmail.com

**Abstract:** Celiac disease is a chronic immune-mediated disorder of the small intestine induced commonly by dietary wheat, barley and rye. It may coexist with autoimmune liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Our study revealed: 1) Isolated hyper transaminasemia with nonspecific histologic changes on a liver biopsy is the commonest hepatic presentation. 2) Liver function test abnormalities affect patients with classical CD or may be the sole presentation of atypical CD. 3) The most common age of presentation was 5 – 10 years with mean age of presentation of 9.47 years.4) There was male predominance with 1.63:1. M: F ratio 5) In the younger children <5 years of age, diarrhea was the most common presenting symptom whereas in the older children i.e. >10 years failure to thrive was the commonest presenting symptom.6) Transaminases were raised in (37.93%) cases. The rise in transaminases was less than 2 times upper limit of normal in 9 cases. 7) After 6 months of gluten free diet, ALT & AST came to be normal in 8 (72.72%) patients while in 3(27.27%) patients, the enzymes declined but were still higher than normal. Our observations suggest that elevated transaminase is common in patients with Celiac disease but recover on gluten free diet. 8)None of the patients had deranged bilirubin.9)Institution of gluten free diet resulted in dramatic clinical improvement with disappearance of GI symptoms like loose stools, pain abdomen and abdominal distension , improvement in appetite, weight and height gain. There was a significant weight and height gain of 4.49 ± 2.32 Kg and 4.61± 2.72 cm on 6 months of gluten free diet.10)Anemia was seen in 23 (88.46%) cases. 9(31.03%) had severe anemia(Hb<8 g/dl), 6 (20.69%) had moderate anemia (Hb 8-10 g/dl) and 8 (27.58%) had mild anemia(Hb 10-12 g/dl).
**Keywords:** Celiac disease, transaminase, Anemia

## INTRODUCTION:

Persistent elevation of serum aminotransferases is the commonest liver abnormality found in untreated Celiac Disease (CD) which in most adults is reversible with a gluten free diet [1, 2]. Conversely up-to 9 % of patients with a persistent and cryptogenic elevation of serum aminotransferases activity may be affected by an asymptomatic CD [3]. Secondly , celiac hepatitis has only mild, nonspecific histological changes including Kupffer cell hyperplasia , mild lobular and portal tract inflammation or steatosis and there is a higher than expected incidence of chronic hepatitis, primary biliary cirrhosis and sclerosing cholangitis in celiac disease[4,5].

**Aims and Objectives:**

- To study the abnormality of liver function test (hepatic involvement) in untreated newly diagnosed celiac disease patients as there is paucity of such data in India [2].
- To see the effect of gluten free diet on the hepatic derangement , after six months of gluten free diet.

**Material and methods** - a prospective study was undertaken over a period of 1 Year in the Department of Pediatrics , Dayanand Medical College and Hospital, Ludhiana, to determine clinical (clinical history and examination) and biochemical liver function (AST, ALT, S bilirubin, ALP, albumin, AG ratio) in 29 newly diagnosed untreated CD patients confirmed by the characteristic duodenal

biopsy ,positive IgA anti TtG test and a response to Gluten free diet, in the age group of 1 to 18 years.

**Inclusion Criteria:** Only those who gave informed consent were enrolled as cases.

**Exclusion Criteria**: Preexisting liver disease at present, past or in the family. All patients were asked to follow a strict gluten free diet schedule. A follow up examination was done after 6 months when clinical examination, LFT, haemoglobin and anti TtG was repeated and effect of gluten free diet was evaluated. Those who continued to have deranged LFT were further investigated for other causes of deranged LFT. Appropriate statistical tests were used for final analysis.

**OBSERVATIONS**

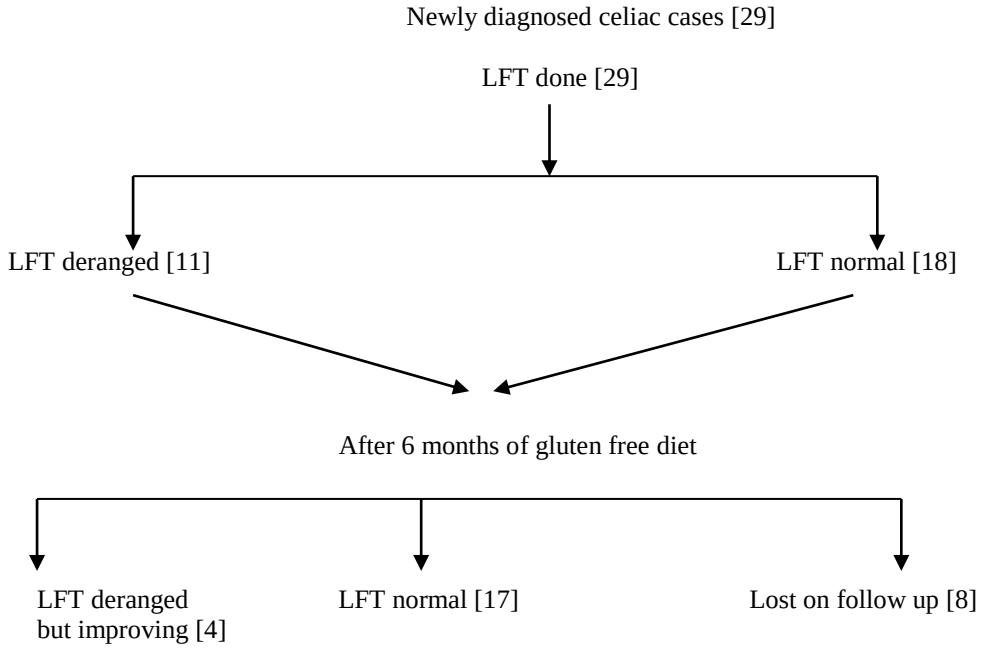


**Table 1: Age and Sex Distribution**

| Age (years) | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | No. | % age | No. | % age | No. | % age |
| <5 | 3 | 16.67 | 1 | 9.09 | 4 | 13.79 |
| 5-10 | 9 | 50.00 | 5 | 45.45 | 14 | 48.28 |
| >10 | 6 | 33.33 | 5 | 45.45 | 11 | 37.93 |
| Mean | 9.14 + 4.30 | | 10.00 ± 4.32 | | 9.47 ± 4.25 | |
| p-value | 0.316278 | | | | | |

Table 1 shows age & sex distribution of subjects. Out of total 29 cases, enrolled in the study maximum cases(14) were in age group of 5 – 10 yrs, followed by 11 in age group of >10 yrs and 4 in age group <5 yrs. Mean age of presentation was 9.47 yrs. Results showed male predominance with male to female ratio 1.63 :1.

**Table 2 Shows distribution of cases according to chief complaints**

| Chief Complaints | <5 years | | 5-10 years | | >10 years | | Total | |
|---|---|---|---|---|---|---|---|---|
| | No. | %age | No. | %age | No. | %age | No. | %age |
| Loose stools | 2 | 50.00 | 4 | 28.57 | 1 | 9.09 | 7 | 24.14 |
| Vomiting | 2 | 50.00 | 1 | 7.14 | 0 | 0.00 | 3 | 10.34 |
| Pallor | 1 | 25.00 | 4 | 28.57 | 2 | 18.18 | 7 | 24.14 |
| Abd Distension | 1 | 25.00 | 5 | 35.71 | 1 | 9.09 | 7 | 24.14 |
| Failure to thrive | 1 | 25.00 | 11 | 78.57 | 10 | 90.91 | 22 | 75.86 |

Table 2: Shows distribution of cases according to chief complaints. Out of 29 cases, maximum cases (22) presented with failure to thrive, followed by loose stools, pallor and abdominal distension and least presented with vomiting. Most common presenting complaint in age group <5 yrs was loose stools and vomiting, while in 5 – 10 yrs and > 10 yrs category , failure to thrive was main complaint.

**Table 3: Distribution of subjects according to Hepatomegaly**

| **Liver palpable** | **No.** | **% age** |
|---|---|---|
| Not palpable | 27 | 93.10 |
| Significantly palpable | 2 | 6.90 |
| p- value | 0.004841 | |

Table 3: shows distribution of cases according to hepatomegaly. Liver was significantly palpable in only 2 cases (p-value-0.004841).

**Table 4: Distribution according to SGOT levels and effect of gluten free diet on SGOT levels**

| **Sgot level (u/l)** | **Basal(29)** | | **After 6 months(21)** | |
|---|---|---|---|---|
| | **No.** | **%age** | **No.** | **%age** |
| 0-40 | 16 | 55.17 | 18 | 62.06 |
| 41-100 | 11 | 37.93 | 3 | 10.31 |
| 100-150 | 0 | 0.00 | 0 | 0.00 |
| 150-200 | 0 | 0.00 | 0 | 0.00 |
| Not done | 2 | 6.90 | 8 | 27.58 |
| Mean | 39.67 ± 12.71 | | 34.49 ± 6.88 | |
| P-value | 0.099935 | | | |

Table 4: Shows distribution of subjects according to SGOT levels. Out of 29 cases, 16 had normal levels, 11 had deranged levels and in 2 SGOT was not done. After 6 months of gluten free diet, 18 had normal levels, 3 had deranged levels but improving and 8 were lost on follow up. Results were slightly significant.

**Table 5: Distribution of Subjects According To SGPT Levels and Effect of Gluten Free Diet on SGPT Levels**

| **SGPT Level (U/L)** | **Basal** | | **After 6 Months** | |
|---|---|---|---|---|
| | **No.** | **%age** | **No.** | **%age** |
| 0-40 | 18 | 62.07 | 17 | 55.47 |
| 41-100 | 10 | 34.48 | 4 | 13.73 |
| 100-150 | 1 | 3.45 | 0 | 0.00 |
| 150-200 | 0 | 0.00 | 0 | 0.00 |
| Not done | 0 | 0.00 | 8 | 27.58 |
| Mean | 39.69 ± 22.44 | | 31.31 ± 13.67 | |
| p-value | 0.110904 | | | |

Table 5: Shows distribution of subjects according to SGPT levels. Out of 29 cases, 18 had normal levels and 11 had deranged levels. After 6 months of gluten free diet, 17 had normal levels, 4 still had deranged levels but showed decreasing trend and 8 were lost on follow up. Results were not significant.

**Table 6: Distribution of Subjects According To TtG Levels and Effect Of Gluten Free Diet On TtG Levels After 6 Months**

| **TTG Level (U/ML)** | **Basal (N=29)** | | **After 6 Months (N=18)** | | **p-value** |
|---|---|---|---|---|---|
| | **No.** | **%age** | **No.** | **%age** | |
| <=10 | 0 | 0.00 | 5 | 27.28 | 0.008543 |
| 10-100 | 9 | 31.03 | 12 | 66.67 | 0.041176 |
| 100-200 | 13 | 44.83 | 1 | 5.56 | 0.009021 |
| >200 | 7 | 24.14 | 0 | 0.00 | 0.043367 |

Table 6: Shows effect of gluten free diet on TTG levels after 6 months of gluten free diet. Initially TTG was >10 in all cases (Total number of cases = 29). After 6 months, all showed fall in levels of TTG. TTG was done in 18 cases, out of which 5 showed TTG.

**Table 7: Distribution of Subjects According To Duodenal Biopsy**

| Biopsy | No. | %age |
|---|---|---|
| Type I | 0 | 0.00 |
| Type II | 0 | 0.00 |
| Type IIIA | 3 | 10.34 |
| Type IIIB | 1 | 3.45 |
| Type IIIC | 21 | 72.41 |
| Type IV | 0 | 0.00 |
| Not done | 4 | 13.79 |

Table 7: Shows distribution of subjects according to duodenal biopsy. Out of 29 cases, maximum showed Type IIIC (as per Marsh classification) 72.41%, followed by Type IIIA -10.43% and Type IIIB 3.45%. 4 cases refused duodenal biopsy.

**Table 8: Distribution of Subjects According To Hb Levels**

| Hb Level(g/dl) | No. | %age |
|---|---|---|
| <8 | 9 | 31.03 |
| 8-10 | 6 | 20.69 |
| 10-12 | 8 | 27.58 |
| >12 | 3 | 10.34 |
| Not done | 3 | 10.34 |
| P –value | 0.084615 | |

Table 8: Out of 29 cases, 23 cases had anemia. 9 had severe anemia, 6 had moderate anemia, 8 had mild anemia and 3 had no anemia. In 3 cases Hb analysis was not done.

**Table 9: Effect of Gluten Free Diet on Weight Gain after 6 Months**

| Age(yrs) | Total | Weight gain (Kg) | | | | | |
|---|---|---|---|---|---|---|---|
| | | <2Kg | | 2 – 4 Kg | | >4Kg | |
| | | No. | %age | No. | %age | No. | %age |
| <5yrs | 2 | 0 | 0.00 | 2 | 100.00 | 0 | 0.00 |
| 5-10yrs | 11 | 1 | 9.09 | 3 | 27.27 | 7 | 63.64 |
| >10yrs | 10 | 0 | 0.00 | 3 | 33.33 | 7 | 70.00 |
| Total | 23 | 1 | 4.55 | 8 | 36.36 | 14 | 60.86 |

| | Basal | After 6 month | Weight Gain(Kg) |
|---|---|---|---|
| Mean weight | 25.15 | 29.64 | 4.49 |
| SD | 11.15 | 11.81 | 2.32 |
| p-value | 0.127251 | | |

Table 9: Shows effect of gluten free diet on weight after 6 months. Out of total 29 cases, enrolled in study, 23 had follow up. In age group <5yrs weight gain was between 2-4 Kg and above 5 yrs weight gain was >4 Kg. Mean weight gain after 6 months was 4.49 Kg (p-value- 0.127251).

**Table 10: Effect of Gluten Free Diet on Height Gain after 6 Month**

| Age (years) | Total | Height gain (cm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | <2 | | 2– 4 | | >4 | |
| | | No. | %age | No. | %age | No. | %age |
| <5 | 2 | 0 | 0.00 | 0 | 0.00 | 2 | 100.00 |
| 5-10 | 11 | 0 | 0.00 | 5 | 45.45 | 6 | 54.55 |
| >10 | 10 | 1 | 11.11 | 5 | 55.56 | 4 | 40.00 |
| Total | 23 | 1 | 4.34 | 10 | 43.47 | 10 | 52.17 |

| | Basal | After 6 m | Height Gain(cm) |
|---|---|---|---|
| Mean height | 126.41 | 131.02 | 4.61 |
| SD | 21.44 | 20.76 | 2.72 |

| | |
|---|---|
| p-value | 0.227733 |

Table 10: Shows effect of gluten free diet on height after 6 months. Out of total 29 cases, enrolled in study, 23 had follow up. In age group <5yrs height gain was >4 cm, 5 – 10 yrs height gain was >4 cm and above 10 yrs height gain was 2- 4 cm. Mean height gain after 6 months was 4.61 cm (p-value- 0.227733).

**DISCUSSION:**

Celiac disease commonly known as wheat allergy, a gluten sensitive enteropathy, is a permanent intolerance to dietary wheat gliadin and related proteins that produce intestinal lesions in genetically susceptible individuals (suggested by the occurrence of multiple cases in families). It mostly presents in the form of chronic diarrhea, abdominal distension and failure to thrive. However, liver dysfunction in celiac disease and the remedial effect of gluten free diet on liver function abnormalities was the subject of our study. The mean age of presentation in the present study was 9.47 yrs which correlated well with several studies [6-8]. Monique *et al.;* found in a study including 74 cases, in 36% cases age of presentation was 6 -10 yrs , in 27% between 2 -5 yrs, 26% cases was more than 10 yrs and in 12 % age of presentation was less than 2 yrs(10).Amrinder singh *et al.;* 2004 ,New Delhi found the mean age of the children with atypical CD and typical CD was 10.8 and 8.9 yrs. respectively(11). Mohindra *et al* did a study on 42 diagnosed celiacs in India and found the mean age at onset of symptoms was 2.4 years (range 0.5-10 years ) and mean age at diagnosis was 8.3 years (range 3-14 years ) respectively, and a mean period of delay in diagnosis was 5.9 (range 1-13.5) years [6]. Kalyaci *et al.;* showed among 135 children that the mean age of presentation as 7.2+/-4.6 yr [12]. Puneet *et al.;* at DMC hospital, Ludhiana showed mean age of presentation as 8.92 years among 71 children [9]. Some studies conducted mainly in western countries showed classical age of presentation 9 – 18 months of age and the diagnosis is usually made within 6 months of onset of symptoms. In a study conducted by Luciano *et al.;* age at diagnosis was 1.17 (+/- 0.69) years [13]. Study done by Vitoria *et al.;* showed age of presentation within 1 year of age in 32.6% patients [11]. Another study by Baudon *et al.;* showed age of presentation within 2 year of age in77 % cases(12).This is because in developing countries there are other causes of chronic diarrhea in children and infections are more common in infancy so celiac is missed. Overall there has been a trend for the diagnosis to be made at a later stage from <2 years to >4 years and mean age has been showing increasing trend, because of less typical cases at an older age and also due to a steady rate of diagnosis of cases with a classic clinical picture . There has been a marked increase in late beginning forms and atypical forms [11].

**Sex distribution of celiac disease:**

A study conducted by Llorente *et al.;* showed male: female ratio of 1: 4 [14]. Monique *et al.;* concluded male: female ratio 1:2 in celiac disease [10]. Ivarsson *et al.;* concluded in a study that there is twofold higher risk (RR: 1.9, 95% confidence interval (CI) 1.7-2.1) for coeliac disease in girls as compared to boys suggesting that girls as compared to boys may be genetically more vulnerable to environmental exposures influencing the immunological processes towards coeliac disease [17]. In the present study, male to female ratio was 1.63:1 showing more preponderance of males to celiac disease. Similar results were shown by study done by Poddar U *et al.;* in 2002 in over 50 children which showed male to female ratio of 3:2 [16]. The most likely reason for the reverse trend could be that boys are often brought to hospital with complaints like failure to thrive while girls are neglected, in India.

**Clinical presentation in celiac disease:**

In the present study, the majority of cases presented with failure to thrive followed by diarrhea and pallor. In the younger age group i.e. <5 years, diarrhea was the most common presenting complaint whereas in older children i.e, > 10 years failure to thrive was the commonest presenting complaint. Puneet *et al.;* also showed in their study that diarrhea was common presentation in age <5 years and failure to thrive in >10 years [9]. Previously, the classical form (i.e., CD presenting with diarrhea and malabsorption syndrome) used to be the commonest presentation among children. However, nowadays, CD is diagnosed earlier in the silent or asymptomatic stage and also in atypical forms. As a result of this, the proportion of classical CD in the West has decreased. George et al reported in a study conducted over 193 celiac patients in Netherland that diarrhea, as a presenting feature of CD, is now seen in only 25-50% of cases compared to >80% of cases in the 1970's and 1980's [18]. However the scene in India is different. Diarrhea (Most common presentation) [6, 16]. anemia, failure to thrive and stunted growth are more frequent in India than in the West, reflecting more severe disease that probably correlates with delayed diagnosis. These differences in clinical presentation also suggest that atypical CD in children in India remains undiagnosed.

Puri *et al.;* diagnosed 7 CD out of 14 children as atypical having short stature and refractory anemia [11]. In a recently conducted prospective study by Sharma *et al.;* over a period of two years, diagnosed atypical CD in 44% of 42 children substantiating need for wider search [19]. An Indian study conducted by Poddar *et al.;* in PGI Chandigarh showed similar results. In this study, predominant symptoms were pallor in 96%, failure to thrive in 92%, and diarrhea in

80%. On follow-up (19.6 +/- 8 months), symptoms subsided within 16 +/- 9.8 days [16]. Canales *et al.;* concluded in a study that cases younger than 10 years presented digestive manifestations such as chronic diarrhea and abdominal distension. Twenty one percent of older patients had atypical presentations (short stature, refractory anemia [20]. A retrospective study conducted over a time period from 1986 to 2003 in USA by Telega *et al.;* 143 patients were diagnosed with celiac disease. Gastrointestinal symptoms dominated in children younger than 3 years, whereas in children older than 3 years, the majority presented with non-gastrointestinal indications [21]. Monique *et al.;* conducted a study including 74 children out of which 69 presented with symptoms. The most common symptoms in younger children (<5 years) were diarrhea (59%), irritability (34%) and weight loss (38%). In older children (>5 years), most common presenting complaint was abdominal pain (55%) followed by diarrhea (20%) [10].

In the present study, the mean weight at presentation was 25.15 +/- 11.15 kg which increased to 29.64 +/- 11.81 Kg after 6 months of gluten free diet. The average weight gain was 4.49kg after 6 months of gluten free diet. On paired t test analysis, weight gain at 6 months was not significant (p-value-0.12). A significant weight gain after introduction of gluten free diet was documented by Nath *et al.;* Fagundes *et al.;* and Rea *et al.;* [22-24].

Poddar et al conducted a study which showed significant weight gain (mean weight at diagnoses and at last follow-up visit were 66% and 86% of expected, respectively; P < 0.001) and height gain (mean height at diagnoses and at last follow-up visit were 88% and 94% of expected, respectively; P = Nonsignificant) [16]. Monique *et al.;* conducted a study which showed 5% of the children with celiac disease had a weight SD score of more than 2SD below the mean and 12 % of children had a height SD score of more than 2 SD below the mean [10]. In the present study mean height at presentation was 126.41 ± 21.44 cm. This increased to 131.02 ± 20.76 cm at 6 months of gluten free diet. On paired t-test analysis, the mean height gain 4.61 ± 2.71 cm was statistically not significant (p<0.22). Podder *et al.;* also showed similar results [16]. A study conducted by Luciano *et al.;* showed that at diagnosis patients had a general tendency to short stature: mean height was 81.8 cm ± 22.9 cm (SDS -0.75 ± 1.61), while target height was 164.3 cm ± 13.5 cm (SDS -0.14 ± 1.04) and final height 169.2 cm ± 7.7 cm (SDS 0.41 ± 1.04). Linear regression and correlations between SDS of final height and age at diagnosis, SDS of height at diagnosis and SDS of target height, respectively, proved Nonsignificant [13].

**Diagnostic criteria of celiac disease**

In present study, TTG level analysis was done in all. The mean anti-tissue transglutaminase level was 153 U/ml. In present study cases were further confirmed by duodenal biopsy and response to gluten free diet. Maximum cases (72.41%) showed total villous atrophy followed by partial villous atrophy in10.34%. Although both the EMA and anti-TtG antibodies are highly specific indicators of celiac autoimmunity, Anti TTG is considered to be most sensitive and specific [3, 4]. According to the (ESPGHAN) gold standard criteria only intestinal biopsy changes and clinical response to GFD are sufficient to make the diagnosis of CD [6]. However, as per modified ESPGHAN criteria [7]. gluten challenge is required when CD is diagnosed in children <2 years of age as many conditions like cow's milk protein intolerance, post enteritis syndrome, and transient gluten intolerance can produce enteropathy. Therefore, in developing countries, villous atrophy is not always synonymous with CD. However, in our experience, sub-total villous atrophy was usually synonymous with the diagnosis of CD.

In present study 29 cases were enrolled, in 3 Hb analysis was not done , 3 had no anemia and 23 had anemia, out of which 9 had severe anemia (Hb<8g/dl), 6 had moderate anemia and 8 had mild anemia. Overall mean Hb value was 9.1 g/dl. Similar results were seen in studies conducted by Mohindra *et al.;* [6], Poddar U *et al.;* [16]. Puri *et al.;* in Delhi included total 12 cases, out of which seven had atypical presentation .Significant anemia was present in 6 of these 7 children and the mean hemoglobin was 7.9 g/dL. Anemia was suggestive of iron deficiency in all 6 children with low serum iron levels and elevated total iron binding capacity [11]. Puneet *et al.;* concluded in a study that out of 43 cases , 20 cases had mild to moderate anemia and 11 patients had severe anemia [9]. In present study, all cases showed clinical improvement after 6 months of gluten free diet.

Hypertransaminasemia has been reported in 54% of children with a classical presentation of CD at the time of diagnosis [46]. Conversely, CD is present in about 9% of patients with chronic unexplained hypertransaminasemia. In the present study, SGOT & SGPT levels were deranged in 37.93% patients. After 6 months of gluten free diet, SGOT levels were normal in 18 cases (62.06%, p-value-0.09), SGPT levels showed decreasing trend but were still deranged in 13.73 % cases (p-value-0.11). A gluten-free diet normalizes liver enzymes and histologic changes in most patients. Bonamico *et al.;* AST was more often abnormal [26].The present study also showed equally affected AST and ALT levels. A GFD leads to normalization of serum transaminases in 75% to 95% of patients with CD and all the liver biopsies normalized after

adherence to a GFD, usually within a year of good adherence to the diet [27, 6, 8].

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