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Effect Of Gluten Free Diet on Outcome of Liver Disease Among Patients of Celiac Disease-A Prospective Study

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Abstract
Background: *Liver involvement in celiac disease is not precisely known in India. Liver involvement of celiac disease has wide spectrum of manifestations.*
Aims & Objective*: To know the effect of gluten free diet on outcome of liver disease among patients of celiac disease.*
Materials & Method*: Out of 94 patients attending gastroenterology OPD who have celiac disease 39 patients diagnosed as liver disease, correspondence to 41.5%. Diagnose of celiac disease is done on Modified ESPGAN criteria. Among patients on follow up with gluten free diet on these patients, there is significant improvement in Gastro intestinal symptoms, extra intestinal symptoms and signs. Same trend was also shown in Blood parameters such as hemoglobin, MCV, MCHC, Platelets counts.*
Conclusion: *Liver involvement in celiac disease is underestimated and potentially treatable cause of Liver Failure. We strongly recommend screening of liver disease among cases of celiac disease and strict gluten free diet to prevent further progression of liver damage.*

I. Introduction

Celiac disease is not newer disease on the globe[1]. In India initial reports of celiac disease from wheat's eating area of Punjab [2], and first accurately described from New Delhi in 1960[2]. The exact incidence of celiac disease in India is not processor known[3].

These are many factors responsible for signs & symptoms of celiac disease.

1. Presence of literary of Gluten. Gluten protein gliadins & glutens show high content of ammo acids like glutamine (32-56%) & proline [4]. Storage proteins similar to gliadins are also found in rye (secalines) and barley(hordeins).[5]
2. Genetic susceptibility – autosomal dominant with incomplete penetance resulting in a disease prevalence of 15% in first degree relative[6], 75% in monozygotic twins [7.] Celiac disease shows HCA class II antigens DQ2 & DQ8 on chromosomes 6p21. The presence of DQ2 or DQ 8 is necessary for the development of celiac disease. [8]
3. Breastfeeding: Breastfeeding during introduction of gluten containing foods has protective effects. [9]
4. Amount of dietary gluten : Increased consumption of a large amount of gluten containing food during instance is likely to increase the risk of celiac disease[10]
5. Age at introduction of gluten – It is beneficial to in introduce gluten at 4 to 6 months of age. As compared to both earlier and late introduction.
6. Infections – Children who experienced 3 or more infections episode before 6 months has increased risk for celiac disease
7. Intrauterine Environment; Increased risk for celiac disease is associated with IUGR & intrauterine Infections. [11]
8. Season at the time of birth: incidence data in 2003 found that there is higher risk for celiac disease in children born during summer as compared to winter. [12]
9. Gender-Girls are likely to be genetically more vulnerable To environment expose that influence the immunological processes leads to Celiac diseaase.[13]
10. Socio economic background -children belong to lower as compared to middle and upper socioeconomic strata of Swedish society has increased risk for CD. [14]

Liver involvement in celiac disease

Liver involvement in celiac disease has wide spectrum of manifestations from an asymptomatic isolated elevation of hepatic transaminases (most common) to severe liver disease insults like the chronic liver disease , acute liver failure and end stage liver disease.[15]

Liver injuries may represent spectrum of the same disorder, where host factors such as genetic predisposition as well as environmental factors like duration of exposure to gluten may collectively influence the severity of liver damage and final outcome.

Celiac disease is an important cause of hypertrasnsaminases. Indeed, has been reported in about 40% of adults & 54% of children with a classical presentation of celiac disease at time of diagnose [16,17].Gluten free diet leads to normalization of serum transaminases in 75% to 95 % patients with celiac disease especially with isolated hypertransaminasemia, usually within a few months of good adherence to the diet. [16-19,20-22.] This consideration recommends us to see the effect of Gluten Free diet as outcome in liver disease among patients of celiac disease.

II. Materials And Methods

Study design: This was institutional based study conducted in department of medicine along with collaboration of dept of Gastroenterology SPMC Bikaner.

Study period: from September 2013 to October 2014

Sample size: All the patients attending one a year period with celiac disease willing for study.

Study area: Patients attending OPD/WARDS in medicine and Gastroenterology at PBM Hospital.

Inclusion criteria

A. All patient diagnosed celiac disease on the base of modified ESPGAN criteria.[23] (European society of Pediatric Gastroenterology and Nutrition)

1. Demonstration of characteristic histological changes on small intenstinal biopsy while on gluten containing diet.

2. Unequivocal clinical improvement on GFD

B. Serology – IgA tTG Ab test (cut off <10ULml)

C. Condition micking celiac disease have been rule out diagnosis of liver disease [24].

1. Clinical signs & symptoms – parotid swelling, clubbing, gynaecomastia, spider naevi etc.

2. Laboratory parameters – Hypoalbuminemia with reversal of A/G ratio
-PTINR (>5 sec)
-One or more episodes of hepatic encephalopathy

3. USG abdomen- coarse echo texture, shrunken liver nodular liver, Portal vein and splenic vein dilatation and splenomegaly, collaterals.

4. Patients with consent.

5. Patients who were well motivated to follow strict GFD

Exclusion criteria;

1. Patients with other known cause of liver disease such as alcohol , viral, autoimmune, toxic , Wilson, heamochromatosis

2. Patients not willing for informed unsent

3. Patients not motivated to follow strict GPD

4. Terminally ill patients

Informed written consent is taken from all patients. All Patients of celiac disease were thoroughly examined clinically and investigated

1. Complete blood count

2. Renal function test

3. Liver function test

4. Pbf, Esr

5. Iga Ttg

6. Ugi Endoscopy For Duodenal Biopsy

7. Hbsa, Hiv, Hcv

8. Autoimmune Markers (Ana)

9. Serum ceruplasmin

Inclusion & Exclusion criteria applied to both groups all the batches Follow up to standard treatment 6 months gluten free diet withStandard treatment.

III. Statistical analysis

All data was analyzed by statistical package for social sciences (SPSS CHICAGO-10) statistical software. The mean value of discrete variables was calculated along with their 95% confidence interval or percentages. Then, data was processed using the chi-square test, student's t-test.

IV. Results

In present study, we screened 94 patients of celiac disease and we found 39 (41.5%) patients has liver disease, so follow up was done with gluten free diet on 39 patients.

Table 1 Prevalence of liver disease in celiac disease patients

Parameter	No	%
Total Number of patients screened	94	100.00
Patients with Celiac with liver disease	39	41.5

The age distribution in 39 patients was maximum in age group 21-30 year contribute to 51.3%

Table 2 Frequency of Age

Age Group(in years)	Frequency	Percentage
<20	9	23.1
21-30	20	51.3
>30	10	25.6
Total	39	100

In our study maximum patients are male contribute to 31 (9.5%)

Table 3 Frequency of Sex

Sex	Frequency	Percentage
Female	8	20.5
Male	31	79.5
Total	39	100.00

On comparison of gluten free diet on these patients for 6 months. The following parameters are compared.

Table 4 Comparison of Prevalence of Gastrointestinal Symptom on Admission an on follow up

GI Symptoms	On Admission		follow up		X2	P
	No	%	No	%		
Diarrhea	4	10.3	3	7.7	0.156	>0.05
Constipation	11	28.2	8	20.5	0.626	>0.05
Vomiting	11	28.2	7	17.9	1.155	>0.05
Pain Abdomen	8	20.5	6	15.4	0.348	>0.05
Abdominal Distension	23	59.0	2	51.1	5.960	<0.001
Decrease Appetite	27	69.2	2	5.1	34.306	<0.001

Comparison of GI symptoms on admission & follow up on GFD, Highly significant difference is seen in abdominal distension & decreased appetite ($p<0.001$).

Table 5 Comparison of Prevalence of extraintenstinal Symptoms on admission and on follow up

Extra intestinal Symptoms	On Admission		follow up		X2	P
	No	%	No	%		
Hematemesis	5	64.1	7	17.9	17.168	<0.001
Melena	25	64.1	8	0.5	24.836	<0.001
Generalized Swelling	5	12.8	0	-	5.342	<0.05
Jaundice	13	2.6	0	0	15.600	<0.001

On comparison of extraintenstinal Symptoms on admission and follow up on GFD, there was significant difference seen in Hematemesis, malena, Jaundice ($p<0.001$), significant difference was found in generalised sswelling ($p<0.05$).

Table 6 Comparison of generalized physical Examination on admission & on follow Up.

General Physical Examination	On Admission		follow up		X2	P
	No	%	No	%		
Pallor	39	100	32	82.1	7.690	<0.01
Pedal edema	7	17.9	0	0	7.690	<0.01
Hair changes	37	94.9	17	8.7	20.513	<0.001
Icterus	13	.33.3	4	10.3	6.092	<0.05
Abdominal Distension	23	59.0	2	5.1	25.960	<0.001
Engorged Veins	13	33.3	2	5.1	9.987	<0.01

There is significant changes seen for pallor, pedal edema ,Hair changes , icterus, abdominal distension & engorged veins suggesting importance & gluten free diet in these patients.

Table 7 Statistical analysis of Hematological examination on admission and on follow up

Hematological examination	On Admission		follow up		T	P
	Mean	SD	Mean	SD		
Hemoglobin(gm)	6.10	1.39	6.78	1.41	4.503	<0.001
MCV(μm^3)	66.81	8.56	87.70	6.39	11.341	<0.001
MCHC(g/dl)	19.84	3.74	30.46	1.83	14.736	<0.001
MCH(pg)	27.15	3.42	28.53	3.21	2.834	0.008
TLC (thousands)	5.44	1.60	5.71	2.01	0.713	0.481
Neutrophils	56.59	12.67	61.96	6.40	2.301	0.028
Lymphocytes	37.00	11.14	29.31	4.76	3.525	0.001
Platelet Count (lacs)	0.95	0.29	1.34	0.39	6.168	<0.001
ESR	38.17	12.79	33.75	8.92	1.421	0.165

Comparison of hematological parameters on admission and follow up on GFD significant improvement is seen in hemoglobin, MCV,MCHC & platelets(p value <0.001).

Table 8 Statistical analysis of liver function test on admission and on follow up

Liver function Test	On Admission		follow up		T	P
	Mean	SD	Mean	SD		
SGOT(IU)	143.06	30.95	39.43	25.26	13.814	<0.001
SGPT(IU)	135.25	21.23	50.62	23.56	11.254	<0.001
SAP(IU)	349.43	103.16	244.00	116.04	2.342	0.003
Total Bilirubin(mg/dl)	3.21	0.73	1.06	0.27	15.413	<0.001
Direct Bilirubin(mg/dl)	1.30	0.32	0.36	0.25	13.612	<0.001
Indirect Bilirubin(mg/dl)	1.94	0.53	0.70	0.16	11.841	<0.001
Total Protein(g/dl)	3.81	0.49	5.24	0.55	12.950	<0.001
Serum Albumin(g/dl)	2.29	0.29	3.26	0.56	8.449	<0.001
Prothrombin Time(in secs)	26.37	5.58	16.87	2.84	8.748	<0.001
INR	2.02	0.42	1.29	0.21	8.805	<0.001
Child Pugh Score	10.12	1.09	6.31	0.93	16.514	<0.001

Comparison of liver function test on admission and follow up on GFD significant improvement is seen in SGOT, SGPT prothrombin time, INR. combing all these parameters there is significant improvement in child pugh score.

V. Discussion

Liver improvement in celiac disease is an underestimated and precisely not known. Liver involvement has wide spectrum of manifestation in celiac disease.[16] Ranging from isolated asymptomatic elevation of serum transaminases to chronic liver disease.[19,26-30] . In our study we compared ,GI symptoms general physical funding , extraintenstinal symptoms & signs, Liver function test etc and combing all these , we found out significant improvement in Childs Pugh some which is the marker of prognostic Indicator of severity in liver disease patients.

In our study the prevalence of liver disease involvements is comparable to comparable to study done by Hagender at al [31], Bardella et al [17], Bonamico et al [18], Morillas et al [32] volta et al [33] where the prevalence ranges from 10-60%. Males was more in our study, the probable discrepancy suggest that female seek less medical attention due to lack of awareness and education. In GI symptoms, significant improvement was observed in abdominal distension & appetite

In extra Symptoms , significant improvement was seen in all parameters, almost similar result were seen in study done by Mounajjed et al [34] & general physical signs showed significant improvement in all parameters which is similar to study done by Holtmeier et al [29].

On comparison of Hematological parameters, there was significant improvement in Hemoglobin from 6.10+ 1.39 to 6.78 +1.41g/dl (p<0.001), MCV, & MCHC. The platelet count also showed improvement from mean value of 0.95+0.29 to 1.34+0.39 lacs(P value <0.001).

On comparison of function test, raised serum transaminases is the most common findings and showed significant improvement also in total protein, albumin, PTINR and combing these parameters, child Pugh score significant improvement from 10.22+1.09 to 7.38+1.47 (P<0.001). Similar results on GFD was also observed in study done by Volta et al [19], In 1998 as well as by Bardella et al in 1999[26]. In 2002 Kaukinen et al done a study on 185 finnish patients , and found GFD can prevent progression to hepatic failure, even in cases in which liver transplant was considered [35].

Similar results were also shown by Barber villares et al [36]. All these findings suggest that improvement is associated with immunological factor and genetic predisposition, or may have direct toxicity of gluten protein to liver, the exact pathogenesis is not known but gluten free diet on their patient is the only effective treatment option available. Although we have not shown the antibodies related to liver, may be limiting factor in our study.

VI. Conclusion

We strongly recommended screening of liver disease in case of celiac disease became early diagnosis & treatment with gluten free diet not only delay or stop the progressive of liver disease in these cases but also can improve already damaged liver, even in cases of end stage liver disease.

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