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ORIGINAL ARTICLE

"Histological Recovery Profiles Of Patients With Celiac Disease- An Indian Perspective."

BHASIN T S *, MANNAN R ***, MALHOTRA V **, SOOD N **, SOOD A *, BHATIA P K ******

ABSTRACT

Aim
Celiac disease is characterized by malabsorption, abnormal small bowel structure and intolerance to gluten. The present study was planned to determine the histological recovery profiles of patients with celiac disease especially, north Indians who consume wheat as the staple diet.

Methods
56 patients were selected for the present study, who were diagnosed to have celiac disease on the basis of their clinical profiles (according to the criteria enumerated by the European society for pediatrics gastroenterology and nutrition), serological examination and confirmation on endoscopic biopsy. Repeat biopsies were taken in all 56 cases. Marsh classification was employed to score the biopsies.

Results
The most common histological presentation at the first biopsy was total villous atrophy (Marsh stage IIIc, 83.9%) followed by subtotal villous atrophy (Marsh stage IIIb, 12.5%) and partial villous atrophy (Marsh stage IIIa, 3.6%). At the end of minimum one year of gluten free diet it was observed that 42 cases (75%) of showed some degree of histological down staging. Of these, 26 (46.42%) recovered completely i.e. to marsh stage 0 (normal villous pattern). Also, 14 out of 56 (25%) cases did not down stage, implying a lack of histological recovery.

Conclusions
The study adds to the limited literature which is available on the histological recovery profiles of patients with celiac disease in the Indian population. The study emphasizes on two facts, one, a time dependency of the response of gluten free diet and second, the importance of proper categorization at the initial biopsy, as higher grades lead to therapeutic refraction.

Key Words:
Histological Recovery Profile, Celiac Disease, India, Marsh Classification.

Key Messages
1. Celiac disease is a disorder which is characterized by malabsorption, abnormal small bowel structure, intolerance to gluten (a protein found in wheat and wheat products) and prompt improvement after a gluten free diet
2. It is important to properly categorize (histological grading) at the time of initial biopsy, as higher grades lead to therapeutic refraction. In all such higher grade cases, prompt and strict adherence to a gluten free diet along with shorter follow up duration by the physician in charge is required.

3. The most common histological presentation according to the Marsh classification in the present study was total villous atrophy – stage IIIc followed by sub-total villous atrophy - stage IIIb and partial villous atrophy - stage IIIa.
4. Maximal recovery rates were seen in patients presenting initially with stage IIIa (100%) and minimal recovery rates were seen in patients presenting with total villous atrophy, i.e. Marsh stage IIIc (44.6%). Thus, the patients presenting with lower histological stage showed recovery in a larger percentage of cases.
5. Recovery of the intestinal mucosa with gluten sensitive enteropathy during a gluten free diet continues beyond 9-19 months and is still incomplete after 2-4 years; so recovery rates increase with time.
6. The varied atypical clinical symptoms of the patients with celiac disease call for a greater awareness of this pathology amongst health professionals in the emerging countries in Asian countries, where this is still regarded as a disease of the west.

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BACKGROUND

Celiac disease is a disorder which is characterized by malabsorption, abnormal small bowel structure, intolerance to gluten (a protein found in wheat and wheat products) and prompt improvement after a gluten free diet.[1].

Although celiac disease is still considered to be uncommon among some Asian and African populations [2] its prevalence in India is reported to be on the rise [3].

Surprisingly, follow up data on small intestinal recovery in celiac disease are scarce and contradictory, with paucity of literature on the histological recovery profiles of patients with celiac disease in the Indian population. The present study was planned to determine histological recovery profiles of patients with celiac disease, especially North Indians who consume wheat as staple diet.

Materials And Methods

The present study was carried out in conjunction with the departments of pathology and gastroenterology of our referral centre. 56 patients were selected in the present study who were diagnosed to have celiac disease on the basis of their clinical profiles, serological investigations mainly anti tissue transglutaminase (TTG)) and on confirmation by endoscopic biopsy. The histological confirmation was done on the basis of the Marsh classification [4],[5] [Table/Fig 1]. The histological findings and TTG levels were noted carefully at the time of diagnosis (before initiation of a gluten free diet).

(Table/Fig 1) Marsh Classification-The Histological Spectrum In Celiac Disease

MARSH 0	Normal mucosal architecture, without significant intra-epithelial lymphocytes infiltration.
MARSH I	With normal mucosal architecture shows a marked infiltration of villous epithelium by lymphocytes; arbitrarily defined as more than 30 lymphocytes per 100 enterocytes (Lymphocytic enteritis).
MARSH II	Intraepithelial lymphocytosis and elongation and branching of crypts in which there is increased proliferation of epithelial cells (Lymphocytic enteritis with crypt hyperplasia).
MARSH III	
MARSH IIIa	The villi are blunt and shortened. Samples were classified partial villous atrophy if villous crypt ratio was less than 1: 1 (Partial villous atrophy).
MARSH IIIb	Villi are clearly atrophic, but still recognizable (Subtotal villous atrophy).
MARSH IIIc	Villi are rudimentary or absent, and mucosa resembles colonic mucosa (Total villous atrophy)

These cases (who were initiated on a gluten free diet) were followed up closely over a period of at least one year or more and repeat biopsies were taken; also, TTG levels were noted. A comparison was done

mainly to assess the patient recovery by means of hemoglobin levels, clinical symptoms, serological levels and histological findings in the initial and the subsequent biopsies.

The duodenal biopsies were retrieved by an endoscope from the second part of the duodenum. Four samples were taken and were carefully oriented on filter paper and were fixed in 10% neutral formalin. The sections which were processed, were examined in a double blinded fashion by two pathologists. In case of discrepancy, the opinion of a third pathologist was taken and two concordant observations were treated as final. The data collected was subjected to statistical analysis and p-values were calculated wherever possible.

Results

In the 56 cases of the present study; the age distribution was varied, which ranged from 3-52 years. The mean age in the study group was 20.16±13.38 years. Patients from a younger age group (≤18 years) constituted the largest cohort, comprising of 60.71% of all the cases [Table/Fig 2]. There were 30 males and 26 females in the present study group with a male to female ratio of 1.2:1.

(Table/Fig 2) Age Distribution Among The Coeliac Disease Patients

Age group (years)	Number of patients	Percentage
≤ 10	16	28.57
10 – 20	20	35.71
21 – 30	06	10.71
31 – 40	08	14.28
41 – 50	04	7.14
> 50	02	3.57
Range: 03-52 years		
Mean Age: 20.16±13.38 years		

The most common presenting complaint was diarrhoea (42.8%), followed by abdominal discomfort (37.5%) [Table/Fig 3]. The mean hemoglobin of these patients at presentation was 9.13±1.094 grams/dl, and at the end of at least one year of follow up with a gluten free diet, it was 11.04±1.45 grams/dl. The mean percentage improvement in hemoglobin was 17.2, which was statistically significant.

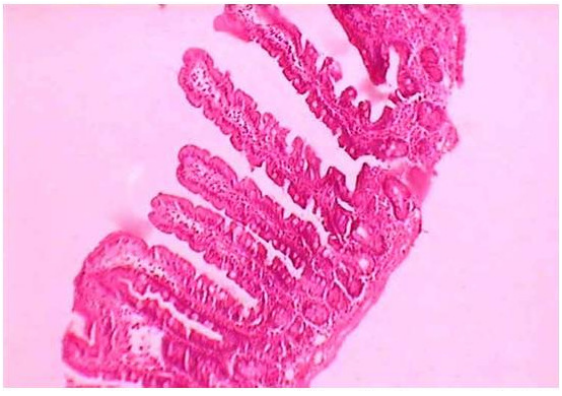
(Table/Fig 3) Distribution Of Clinical Complaints

Presenting complaint at initial biopsy	Diarrhea	Failure to gain weight	Abdominal discomfort / distension	Anorexia
No. Of patients	24	15	21	9
%	42.8	26.7	37.5	16.1

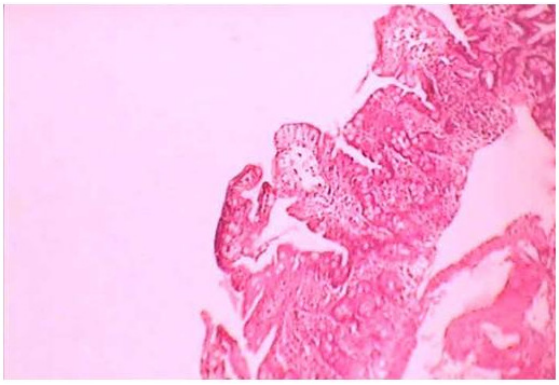
The most common histological presentation at the first biopsy was total villous atrophy (Marsh stage IIIc, 83.9%) followed by subtotal villous atrophy (Marsh stage IIIb, 12.5%) and partial villous atrophy (Marsh stage IIIa, 3.6%). There were no cases of stage 0, I and II of the Marsh classification in all the 56 cases which were included in the present study at the initial **biopsy [Table/Fig 4] (Fig. 1, 2, 3, 4, 5, and 6).**

(Table/Fig 4) Histological Spectrum Of All Biopsies As Per Marsh Classification At First Biopsy.

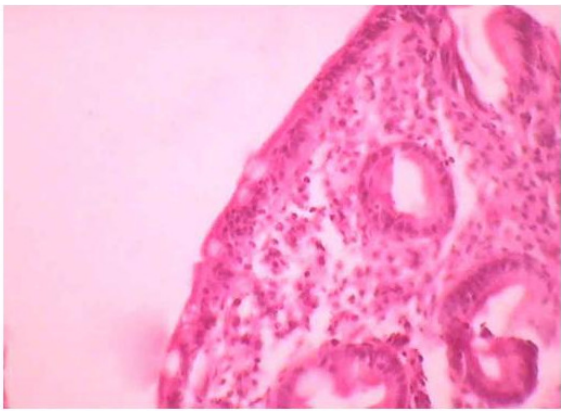
	Marsh Classification					
	Stage 0	Stage I	Stage II	Stage III		
				IIIa	IIIb	IIIc
Ist biopsy	0	0	0	02	07	47
%age	0	0	0	3.6	12.5	83.9



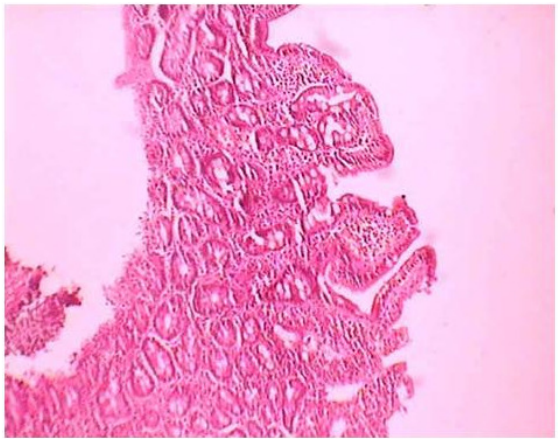
(Table/Fig 4) (Fig 1) Normal villous pattern, Marsh Stage 0 (H & E 100 X)



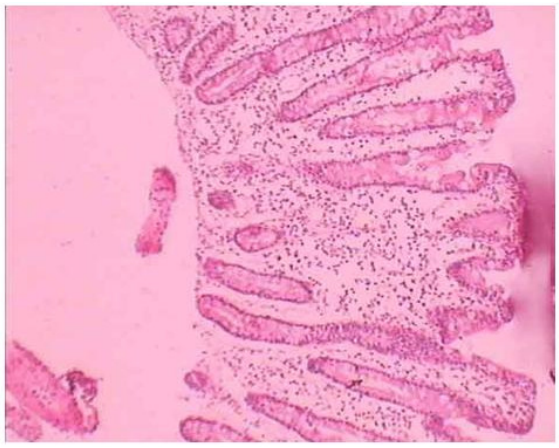
(Table/Fig 4) (Fig 2) Crypt Hyperplasia (H & E 100 X)



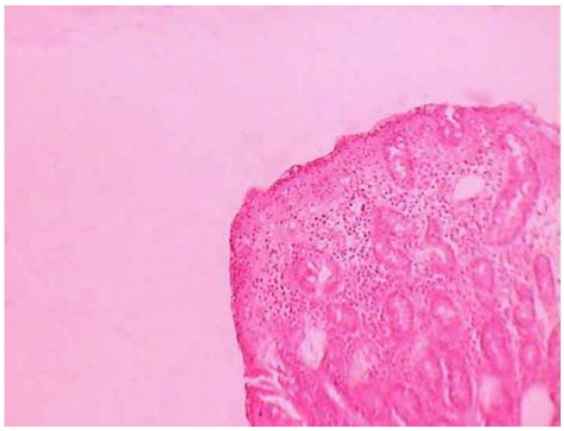
(Table/Fig 4) (Fig 3) Increased intraepithelial lymphocytes (H & E 400 X)



(Table/Fig 4) (Fig 4) Partial villous atrophy Marsh Stage IIIa (H & E 100 X)



(Table/Fig 4) (Fig 5) Sub-total villous atrophy Marsh Stage IIIb (H & E 100 X)



(Table/Fig 4) (Fig 6) Total villous atrophy Marsh Stage IIIc (H & E 100 X)

The mean follow up duration after putting the patients on a gluten free diet was 1.98 years. The majority of the patients (53/56) showed a dramatic clinical improvement, such as gain in weight and relief from diarrhoea along with improvement in hemoglobin levels.

Of the 47 patients who presented with total villous atrophy, (Marsh Stage III c) initially; 19 cases (40.42%) recovered completely and 12 cases (25.53%) remained

at the same stage even after adhering to a gluten free diet for one year [Table/Fig 5].

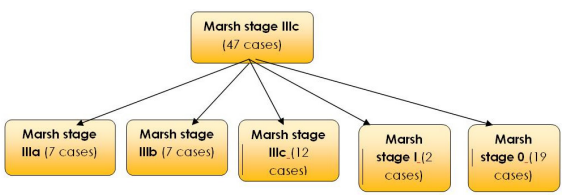
(Table/Fig 5) Histological Spectrum Of All Biopsies As Per Marsh Classification At Second Biopsy

	Marsh Classification					
	Stage 0	Stage I	Stage II	Stage III		
				IIIa	IIIb	IIIc
IInd biopsy	26	2	Nil	07	09	12

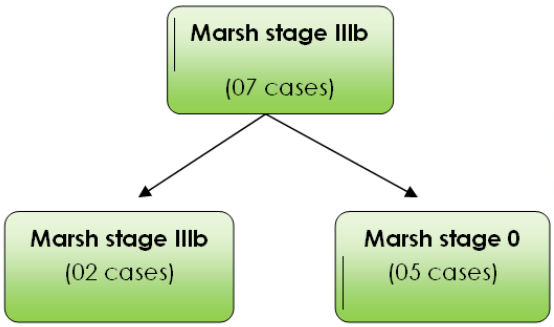
Five (71.42%) out of the seven cases which presented with subtotal villous atrophy, (Marsh Stage III b) initially recovered completely, whereas; two (28.57%) remained at the same stage at the end of one year of follow up. However; both of the cases presenting with partial villous atrophy, (Marsh Stage III a) initially recovered completely.

Thus, at the end of minimum one year of gluten free diet adherence, it was observed that 42 cases (75%) of the total cases showed some degree of histological down staging. Of these, 26 (46.42%) recovered completely i.e. to marsh stage 0 (normal villous pattern). Also, 14 out of 56 (25%) cases did not down stage, implying lack of histological recovery. Maximum recovery rates were seen in patients presenting with stage IIIa (100%) and minimum recovery was seen in patients presenting with total villous atrophy, i.e. Marsh stage IIIc (44.6%). The p values of the recovery profiles in all the three categories are statistically significant [Table/Fig 6],[Table/Fig 7].

(Table/Fig 6) Recovery Profiles Of Patients With Initial Biopsies- March Stage III c



(Table/Fig 7) Recovery Profiles Of Patients With Initial Biopsies –Marsh Stage IIIb



The recovery rate was highest in the age group 41-50 years and males documented better recovery than females [Table/Fig 8],[Table/Fig 9].

(Table/Fig 8) Age Related Recovery Profiles

Age group (years)	No. of patients	No. showing complete recovery	% showing complete recovery	No. showing no recovery	%showing no recovery
<10	16	06	37.5	05	31.25
11-20	20	12	60	06	30
21-30	06	01	16.7	0	0
31-40	08	05	62.5	0	0
41-50	04	03	75	1	25
>50	02	00	00	0	0

(Table/Fig 9) Sex Related Recovery Profiles

	No. of cases	No. showing complete recovery	% showing complete recovery	No. showing no recovery	% showing no recovery
MALES	30	19	63.3	05	16.67
FEMALES	26	11	42.3	06	23.1

No known complications of celiac disease like collagenous sprue or enteropathy associated T-cell lymphoma were documented during the course of the present study.

Discussion

The name sprue was coined in the 18th century and has been derived from the Dutch word 'spruw', which means 'aphthous disease', which was so named

because of the high prevalence of aphthous ulcers in such patients [6].

Thin perhaps gave the first account of the pathological appearances of the small intestine in 'sprue' [7]. Royer and his colleagues in Argentina described a technique for per oral duodenal biopsy by aspiration [8]. Since then, endoscopic biopsy has become a routine procedure for the investigation of celiac patients.

A serendipitituous observation in Netherlands during World War II led to the finding that wheat exacerbates celiac sprue. As the cereals which were used to make bread were particularly scarce, the children with celiac disease improved; only to relapse after the replenishment of cereal supply at the end of the war. Subsequent work showed that it was the water insoluble portion or the gluten moiety of the wheat that produced malabsorption in patients with celiac sprue [9] ,[10].

Celiac disease affects women more commonly than men, with male to female ratio described in the range of 1: 1.3-2 [11]. In our study, male patients were more common, which can be explained firstly, on the basis of higher male to female sex ratio in Punjab and secondly on the probable basis of prevalent social ill of ignoring the female child in resource challenged countries like India.

The most common presenting complaint in the present study was diarrhoea (42.8%), followed by abdominal discomfort /distension (37.5%), as stated in other studies also[12],[13].

After starting a gluten free diet, there was an improvement in the mean hemoglobin as pointed out in earlier studies [14]. Recovery from anemia occurs between six and twelve months after starting on a gluten free diet as a consequence of the normalization of the histological alterations of the intestinal mucosa.

The most common histological presentation according to the Marsh classification in the present study was total villous atrophy – stage IIIc, followed by sub-total villous atrophy - stage IIIb and partial villous atrophy - stage IIIa. These findings are in variance with other studies; including a study conducted in India, where a higher incidence of stages IIIa and IIIb have been quoted [12],[15]. The possible reason for the majority of Indian patients diagnosed in Stage III is, a lack of awareness about celiac disease. Also, these patients generally reach the hospital late as the symptoms are easily confused with those of gastrointestinal infectious diseases, for which over the counter drugs are easily available and/or nutritional deficiencies.

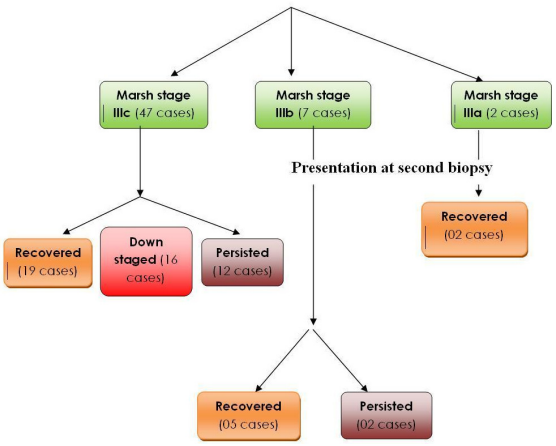
All the patients in our study after the first biopsy were counseled to go on a gluten free diet and were then followed up at monthly intervals. Most of them (53/56) showed dramatic clinical improvement including a fall in TTG levels. Three patients, who had initially responded clinically to a gluten free diet, later relapsed due to non-compliance with a gluten free diet. Literature states that lack of adherence to strict gluten-free diet is the main reason of poorly controlled disease [16]. Dietary compliance as assessed by interview is the best marker for celiac disease control due to low cost, non-invasiveness, and a strong correlation with intestinal damage.

Follow up biopsies taken after a minimal interval of one-year (mean 1.98 years) showed that 46.42 % cases recovered completely i.e. to stage 0 of Marsh classification and 25% patients persisted with villous atrophy (stage IIIc/IIIb) [Table/Fig 10],(Table/Fig 10 and Table/Fig 11) . This is in concordance with the studies conducted by various researchers, noticeably by Ciacci C et al and McNicholl B et al who have showed similar recovery rates and persistent change on repeat biopsy with a gluten free diet [17],[18]. However, the work conducted by Wahab et al reported greater recovery rates in the range of 85.3 % on a gluten free diet [15].

This can be explained by the longer duration of follow up, that is 5 years in these cases, as compared to the mean follow up of 1.98 years in the present study. This very fact is highlighted by the reports by various researchers that the recovery of the intestinal mucosa with gluten sensitive enteropathy during a gluten free diet continues beyond 9-19 months and is still incomplete after 2-4 years; so, recovery rates increase with time [19].

Findings in the present study of maximal recovery rates in patients presenting initially with stage IIIa (100%) and minimal recovery rates in patients presenting with total villous atrophy that is Marsh stage IIIc (44.6%), correlate with the findings observed by other researchers [15]. Thus, the present study also concludes that patients presenting with lower histological stage show recovery in a larger percentage of cases [Table/Fig 10] (Table/Fig 10 &11).

(Table/Fig 10) Final Analysis Of All The Biopsies Of All The Three Stages.



(Table/Fig 11) Comparative Analysis Of Recovery Profiles

STAGE OF FIRST BIOPSY	COMPLETE RECOVERY	NO RECOVERY	P value
IIIc	44.6	25.5	<0.01
IIIb	71.4	28.6	<0.01
IIIa	100	0	<0.05

Also, recovery rates in children are reported to be higher in comparison to that in adults by many researchers [15]. This fact is corroborated in the study undertaken, which shows a higher percentage of complete recovery (50%) as compared to the adult population, which showed complete recovery to the tune of 45.45%.

Long term complications in the cases which were considered to be refractory, show symptoms of active celiac disease. The mortality rate though low, has been reported in such cases. Disseminated enteropathy-associated T-cell lymphomas are known to develop in patients with refractory disease, which is usually not seen in any of the patients with non-refractory disease. No such complications were seen in our study, as these complications are encountered on long-term follow up [20],[21].

Conclusion

A decade ago, celiac disease was considered to be a comparatively uncommon disorder with a prevalence of 1 in 1000 or lower. The greater awareness of its presentation and the availability of new accurate serological tests such as IgA endomysial antibodies, anti tissue transglutaminase and anti glidan antibodies have lead to the realization that it is relatively common, affecting 1 out of every 120-300 persons in Europe and North America [22].

Clinical applications of serological tests include not only the evaluation of patients with suspected celiac sprue depending on their pre-test probability of having the disease, but also the monitoring the adherence and response to a gluten free diet, as well as possibly screening asymptomatic persons for the disease.

The incidence of celiac disease in India is on the rise. The varied atypical clinical symptoms of the patients with celiac disease call for a greater awareness of this pathology amongst health professionals in

the emerging countries in Asian countries where, this is still regarded as a disease of the west.

Literature regarding the histological recovery profile is limited and that too, especially for the Indian sub-continent. The present study adds to the available literature and statistical analysis on celiac disease, by having a substantial sample size (56 cases) and interval (minimal interval of one and a half year).

The study further emphasizes the fact of time dependency on the response of gluten free diet in celiac disease and also, the importance of proper categorization (histological grading) at the initial biopsy, as higher grades lead to therapeutic refraction. In all such higher grade cases, prompt and strict adherence to a gluten free diet, along with shorter follow up duration by the physician in charge is required.

These cases in turn, may be the ones which present with aberrant and neoplastic complications.

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