Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 07, 2024

ORIGINAL RESEARCH

Clinicopathological correlation of duodenal biopsy in patients with malabsorption

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Received: 1 April, 2024 Accepted: 03 May, 2024

Abstract

Background: Malabsorption syndrome affects millions of people in the world and is mostly associated with gastrointestinal (GI) symptoms like pain abdomen, bloating, flatulence, diarrhoea and some extra intestinal manifestations like iron deficiency anaemia, growth retardation, muscle cramps etc. The aetiology of malabsorption varies according to the age of the patient and geographical location.

Aims and Objectives: To study morphological spectrum of duodenal biopsies in patients presenting with symptoms of malabsorption and to correlate the histopathological findings with endoscopic findings and relevant laboratory parameters where ever possible.

Material and Methods: A retro prospective study was done for a period of 3 years and 6 months from January 2019 till October 2022. The study included75 presenting with signs and symptoms of malabsorption. Patients with history of major gastrointestinal surgery were excluded from the study.

Result and Analysis: The patients had a mean age (32.8) years, with male: female ratio to be 04: 1, the most common presenting complaint was pain abdomen (72%) followed by anaemia under evaluation. (24%) The commonest diagnosis in the study was celiac disease (33. 3%). A good correlation was established with Endoscopic and laboratory findings as (45. 27%) cases showed abnormal findings and serological findings (Anti TTG levels) correlated well with celiac disease.

Conclusion: Duodenal biopsy is a useful parameter in corroborating a diagnosis in patients presenting with symptoms of malabsorption. However, significant correlation of biopsy with endoscopic, serologic and hematologic parameters is of utmost importance to reach a final diagnosis.

Keywords: Duodenal biopsy, malabsorption, celiac disease, anti-TTG

Introduction

The gastrointestinal tract in human body is involved in the process of absorption of nutrients like fat, proteins, carbohydrates, vitamins and minerals. Malabsorption is defined as defective mucosal uptake and transport of nutrients across the gastrointestinal tract leading to malnutrition and variety of anemias.[1] Malabsorption differs from maldigestion as former is

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the defect in absorption of nutrients at any point where absorption is taking place, whereas maldigestion is impaired digestion of nutrients with in intestinal lumen /at brush border.[2]
Malabsorption affects millions of people in the world. It is mostly associated with symptoms related to gastro-intestinal tract. A detailed assessment of symptom duration, symptom timing, and presence of aggravating and relieving factors like pain, intensity of symptoms becomes very important while dealing with malabsorption.[3]
Diarrhea remains the most common presenting complaint worldwide. Other symptoms are abdominal pain, flatulence, bloating etc.[4] Patients may also present with some extra intestinal manifestations like anemia, growth retardation, swelling/edema, muscle cramps. Among the nutritional deficiencies, iron deficiency appears to be the most common finding in patients with malabsorption in developing countries like India. Sometimes it may be the only presenting complaint.
However, the proportion of celiac disease and crohn's disease appears to be increasing in developing countries. With the improvement in socio economic status, sanitary conditions and use of antibiotics incidence of tropical sprue has declined. [5]In both children and adults, celiac disease is one of the major cause of malabsorption.[6-11]Some other etiologies include congenital causes, HIV related enteropathies, bacterial etiologies of malabsorption including infections associated with *Giardia lamblia*, *Tropheyrema whipplei*, *Cryptosporidium parvum*, bariatric and resection surgeries.
Prognostically malabsorption syndrome is not a life threatening condition but a number of complications can arise when malabsorption syndrome is poorly controlled or if it persists for a longer duration.[20] Some of its complications include weight loss, malnutrition, Vitamin and mineral deficiencies, hematological complications like anemia and coagulopathies, Dermatologic manifestations like skin changes, Musculoskeletal dysfunction like growth retardation, skeletal deformities as in rickets, Electrolyte disturbances, Neurologic dysfunctions and Endocrine dysfunction.
Management in setting of malabsorption includes correcting the deficiencies, treating the underlying cause and avoiding the trigger factors. The present aim to study morphological spectrum of duodenal biopsies in patients presenting with symptoms of malabsorption& to correlate the histopathological findings with endoscopy and relevant laboratory parameters (wherever available).

Materials and methods

The present study was a cross-sectional study over a 3 years and 6 months done in the histopathology section of Department of Pathology. All duodenal biopsies from patients presenting to the gastroenterology department with signs and symptoms of malabsorption were evaluated. Ethical clearance has been obtained from institutional ethical committee.
Inclusion criteria: 1. All patients clinically presenting with signs and symptoms of malabsorption. 2. Patient with iron deficiency anemia who are not responding to oral iron therapy. Exclusion criteria was patients with history of major gastrointestinal surgery. Total sample size was 75.

Data collection

1. The patients taken for this study were explained about the whole study and an informed consent has been obtained as per the proforma attached. Relevant demographic details, clinical history, and endoscopic findings of the patient was noted as per protocol.
2. Relevant laboratory findings like complete blood counts (CBC), liver function tests (LFT), stool examination, serum micronutrient levels (Serum iron, Vitamin B12, Folate levels) and serological investigations e.g. anti TTG wherever done were noted from the patient's record file.

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3. For the retrospective aspect the slides of the duodenal biopsies were retrieved along with the paraffin blocks from the departmental records. For the prospective aspect the fixed duodenal biopsies were processed as per the standard protocol for the small biopsies. H&E-stained slides were then reviewed.
4. Special stains like Periodic acid–Schiff [PAS], Diastase resistant periodic acid –Schiff [DPAS], Alcian blue periodic acid–Schiff [ALPAS], Acid fast bacilli [AFB] stains were used where ever necessary for both prospective and retrospective studies.
5. The biopsy specimen was evaluated for below mentioned histologic features: The villous and crypt architecture, villous to crypt ratio (V: C ratio), surface enterocytes morphology, intra epithelial lymphocytes (IEL's) count per 100 enterocytes.
6. Inflammation content and extent in lamina propria, presence of infectious etiology like granuloma, luminal parasites, were noted.
7. Assessment for dysplasia or malignancy or any other relevant histological findings were also noted as per the protocol proforma.
8. Modified Marsh classification[12] was used in case of celiac disease in order to classify it into different stages of severity.

Statistical analysis

The data was analyzed by SPSS version 11 for frequency and percentages. Chi square test was used wherever applicable and *p* value of <0.05 was considered statistically significant. As per the protocol relevant demographic details, clinical history, endoscopic findings and laboratory findings were noted and results were analysed.

Results

The age of patients ranged between 3 years to 74 years with mean being 32.8 years. The majority (26.7%) of the study subjects were in the age group 21-30 years followed by 18.7% in the age group 31-40 years, and 16% in the age group of 41-50 years. There was a clear female preponderance (69.33%) in the study group with Male to Female ratio of 0.4:1.

Bloating and pain abdomen was the commonest clinical presentation seen in 54 patients (72%) followed by anaemia, which was seen in 18 patients (24%). Only 2 patients presented with diarrhoea (2.7%) and one presented with upper GI bleed (1.3%).

On the basis of laboratory findings moderate to severe anaemia was observed in 10 cases of celiac disease, 6 cases of intraepithelial lymphocytosis, 1 case of duodenopathy, 1 case of Tubulovillous adenoma, 1 case of intestinal lymphangiectasia and 7 cases having normal biopsy findings. TLC was found to be raised in 4 cases of Celiac disease, 1cases each of duodenitis and 3 cases of duodenopathy, 2 cases of malignancies and a single case showing increase intraepithelial lymphocytosis. LFT were deranged in 5 cases each of celiac disease and 4 cases of intraepithelial lymphocytosis, 1 case of peptic duodenitis and 4 cases having normal biopsy findings.

The mean Haemoglobin (Hb) level in the study group patients was 10.24 ± 1.49 gm%, mean TLC level 12.24 ± 9.81 gm/dl, T. Bilirubin 56 ±0.63, and S. albumin 3.06 ± .51. Mean levels for SGOT and SGPT was 61.20 ± 68.28 and 49.92 ± 67.64. (Fig. 1)

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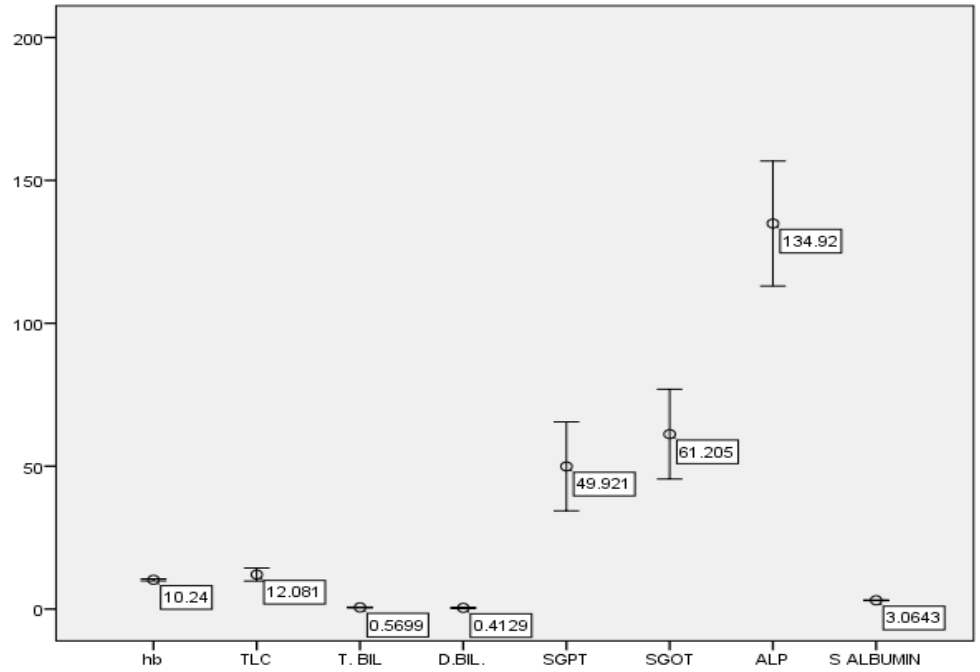
Figure 1: Laboratory findings of the study subjects



Endoscopic findings of the duodenal biopsy in 29 cases (38.7%) were within normal limits. Among the abnormal findings, scalloping of duodenal folds was seen in 17 cases (22.7%) with scalloping and grooving of duodenum seen in 8 cases (10.7%). This was followed by duodenal erosion in 7 (9.3%), mucosal oedema in 5 (6.7%), duodenal growth and hiatus hernia in 3 (4%) each and esophagitis, duodenal polyp and duodenal ulcer in 1 each (1.3%) of the study patients. (Fig. 2)

Figure 2: Different endoscopic findings of the study subjects

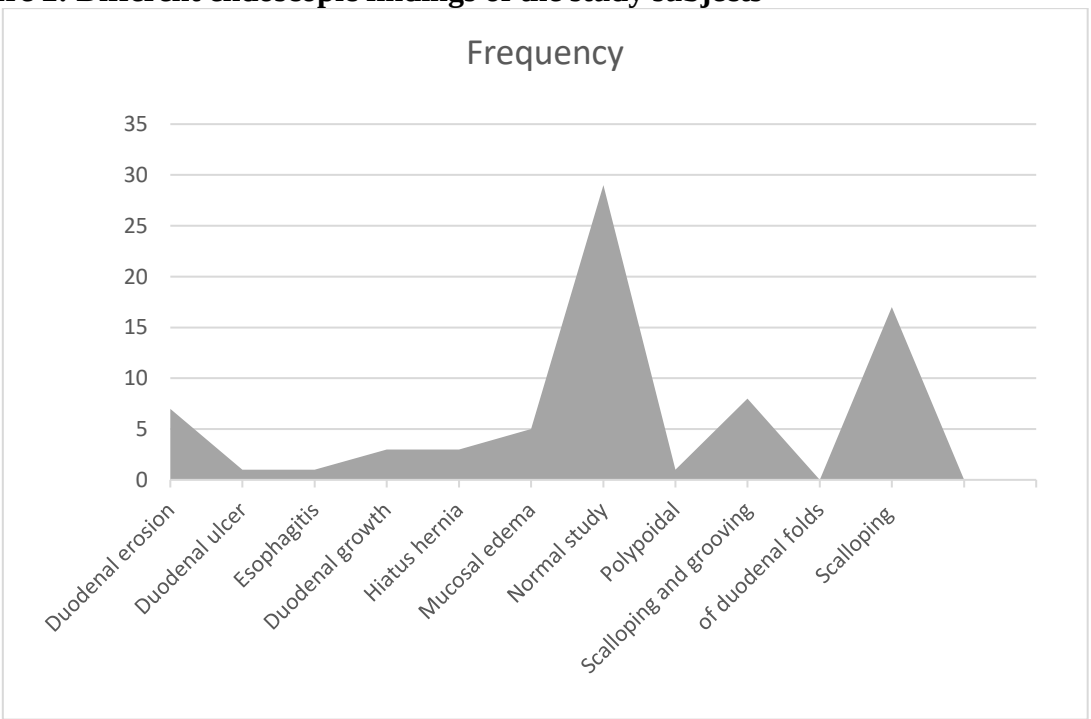


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Table 1: Summary of histopathological findings and spectrum of final diagnosis

Summary of histopathological findings	Final diagnosis	Frequency	Percentage
Normal villous morphology	Within normal limits	14	18.6%
Normal villous morphology	Celiac disease Modified marsh grade 0. (Celiac serology positive)	2	2.6%
Normal villous morphology with increase in Intraepithelial lymphocyte count.	Intraepithelial lymphocytosis (Celiac serology Negative)	16	21.3%
Normal villous morphology with increase in Intraepithelial lymphocyte count.	Celiac disease Modified marsh grade 1 (Celiac serology positive)	8	10.6%
Villous atrophy with crypt hyperplasia and increase in intraepithelial lymphocyte count	Celiac disease Modified marsh grade 3 (Celiac serology positive)	15	20.0%
Presence of tear drop shaped trophozoites along the surface enterocytes of the villi.	Giardiasis	3	4.0%
Normal villous morphology with lamina propria revealing mixed inflammatory infiltrates and dilatation of lymphatics.	Intestinal lymphangiectasia	1	1.3%
Lining epithelium reveals ulcerations and Lamina propria shows mixed inflammatory infiltrates.	Duodenitis	8	10.6%
Normal villous morphology with strips of muscularis mucosae seen insinuating the lamina propria.	Duodenopathy	4	5.3%
Tubulovillous architecture with low grade dysplastic epithelium composed of hyperchromatic elongated nuclei.	Tubulovillous adenoma	1	1.3%
Mucosae infiltrated by neoplastic epithelial cells	Adenocarcinoma/poorly Differentiated malignancy	3	4.0%

Table 1 showed the most common final diagnoses in the whole spectrum was cases of celiac disease 33.3%. 2.6% of these were categorized as Modified marsh grade 0.10.6% were categorized as Modified Marsh grade 1.20% were categorized as Modified Marsh grade 3. Second commonest diagnosis in the study conducted was intraepithelial lymphocytosis [21.3%] cases. Out of 16 cases of intraepithelial lymphocytosis 5 cases were found to be

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having association with H. pylori gastritis and 2 cases were having association with autoimmune thyroiditis.

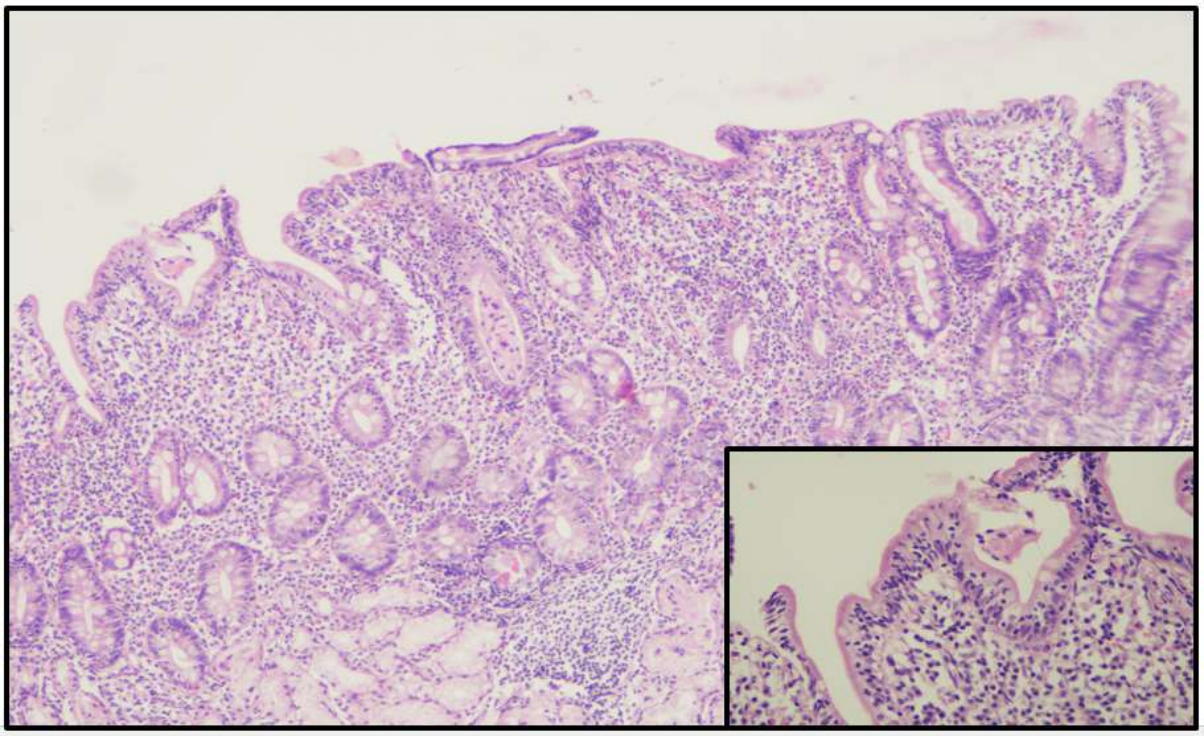

Figure 3. Marked villous atrophy with crypt hyperplasia and increase in IELs corresponding to Modified marsh grade 3C Celiac disease (100x). Inset (400x) H&E stain

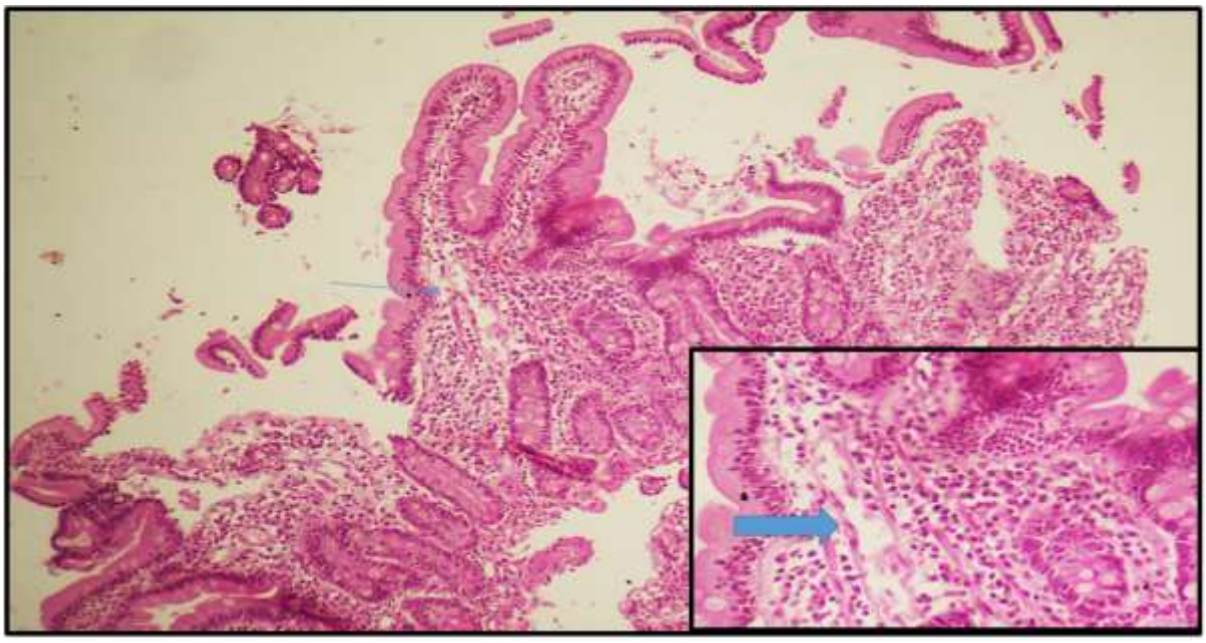

Figure 4. Fibres of muscularis mucosae seen insinuating the lamina propria (arrow) consistent with duodenopathy (x100). Inset (x400) H&E stain

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Table 2: Associations of laboratory findings between celiac and non-celiac disease

	Celiac Category	N	Mean	Std. Deviation	Std. Error Mean	P value
Hb	Celiac	25	10.12	1.666	.333	0.45
	non-celiac	50	10.40	1.414	.200	
TLC	Celiac	24	10.507667	8.4429251	1.7234049	0.29
	non-celiac	50	13.077580	10.3844066	1.4685769	
T. BIL	Celiac	25	.28	.678	.136	0.28
	non-celiac	50	.48	.789	.112	
D.BIL.	Celiac	25	.12	.440	.088	0.30
	non-celiac	50	.28	.701	.099	
SGPT	Celiac	25	47.72	73.902	14.780	0.85
	non-celiac	50	50.98	65.174	9.217	
SGOT	Celiac	25	51.40	53.828	10.766	0.38
	non-celiac	50	66.14	74.523	10.539	
ALP	Celiac	25	137.56	100.664	20.133	0.86
	non-celiac	50	133.48	93.046	13.159	
S ALBUMIN	Celiac	25	3.12	.726	.145	0.35
	non-celiac	50	2.96	.669	.095	
Total protein	Celiac	25	5.92	.572	.114	0.49
	non-celiac	50	5.80	.756	.107	

Table 2 showing Associations of laboratory findings with celiac and non-celiac disease, the mean Hb level for celiac disease was 10.12±1.66, whereas for non-celiac disease it was 10.40±1.41. There was no statistically significant difference between the two groups. TLC in celiac disease group was 10.44±8.41 ($10^{3)}$ and for non-celiac disease was 13.07±10.38, with non-significant difference. Levels of T. Bil, D. Bil, SGOT, SGPT, ALP, S. Albumin and total protein levels both in celiac disease group and non-celiac disease was almost similar an statistically non-significant with p value of 0.28, 0.30, 0.85, 0.38, 0.86, 0.35 and 0.49 respectively.

Table 3: Comparison of clinical presentation in cases of celiac disease and non-celiac disease

		Celiac		Total
		celiac disease	non-celiac disease	
Clinical presentation	Anaemia under evaluation	6	12	18
	diarrhoea	1	1	2
	pain in abdomen	17	37	54
	upper GI bleed	1	0	1
Total		25	50	75
Chi-square value- 2.33, *p* value- 0.51, non-significant				

Table 3 showing an association of clinical presentation with celiac disease. Of the 25 celiac disease patients, 17 had pain abdomen, 6 had anaemia under evaluation, 1 had diarrhoea whereas, in non-celiac disease, 37 had pain abdomen, 12 had anaemia and 1 patient presented with diarrhoea. Despite difference in the numbers no significant difference was noted. (*p* value>0.05).

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Anti TTG levels was done in all the cases presenting with malabsorption irrespective of the duodenal endoscopic findings. The institutional normal range of anti TTG is 0.0-20.0U/ml. In 30.6% of the cases anti TTG levels were within a range of 1-4U/ml, 36% were within a range of 5-10U/ml,9.3% were in a range of 11-50U/ml, 21.3 were in a range of 50-100U/ml and 2.7% were in a range of more than 100U/ml. The Anti TTG levels were raised in a total of 25 patients ranging from 21.1 U/ml to 798.4 U/ml. In 50 patients the Anti TTG levels were not raised, levels were less than 20.0U/ml.

Figure 5: Distribution of study subjects as per serology (Anti-TTG) category

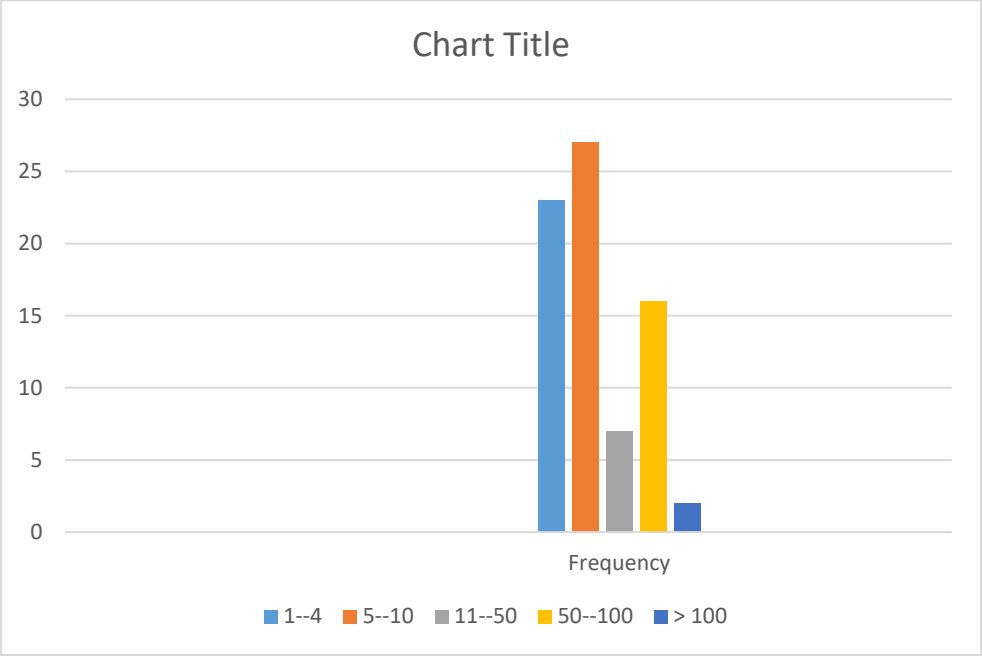

Table 4: Association of Anti TTG level with presence of celiac disease

	VAR00001	N	Mean	Std. Deviation	Std. Error Mean	
Anti TTG Level	Celiac disease	25	84.56	149.898	29.99	T value - 3.79, *p* value - 0.00
	non-celiac disease	50	4.60	2.356	0.34	
	Total	75	31.25			

Table 4 showing association of TTG level with presence of celiac disease, The anti TTG level for celiac disease was 84.63±149.96, whereas for non-celiac disease was 4.61±2.34. The difference between them was statistically significant. (*p* value= 0.0).

Discussion

Upper GI endoscopies are performed in the endoscopic unit for a number of reasons. Patients usually present with common gastrointestinal tract related symptoms but sometimes atypical clinical presentations like weight loss, growth retardation are also common. On duodenal biopsy based on the histopathological features and their correlation with various parameters, a final diagnosis can be made. In the present study the histopathological findings of patients with malabsorption are correlated with various parameters like endoscopic, serologic,

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hematologic findings. A comparative analysis of these parameters of various studies to that of the present study has been done.

The present study reveals most common presenting complaint to be Pain abdomen [54 cases] followed by anaemia [18 cases] which was almost similar to the study done by B. Atilla et al[13] and Emami M et al[14] having commonest presentation as pain abdomen and dyspepsia [104 cases] and [108 cases] respectively. However, the second commonest complaint in these studies was diarrhoea. The present study does not match with studies done by Balasubramanian P et al[15], Husnoo N et al[16]The study reveals comparison of clinical symptoms of various studies having diagnosed with malabsorption with that of the present study.

The present study shows that GI symptoms are commonest presentation in malabsorption [23 cases] followed by anaemia[6 cases].The present study matches with the studies done by Balasubramanian P et al[15],Emami M et al[14] having GI symptoms as a commonest presentation 14 cases and 61 cases respectively. The present study does not match with study done by Mahadev S et al[17].In contrast to the study of Balasubramanian P et al[15] the present study reveals pain abdomen to be the commonest presenting complaint followed by anaemia in the histopathologically and serologically proven cases of celiac disease.

The TTG levels ranged from 1U/ml- 798U/ml in the present study. Two cases in the present study revealed Anti TTG value to be exceeding beyond 100 U/ml. Anti TTG value in various other studies were also high as seen in study done by Alessio et al[18].
The study reveals comparison of endoscopic findings of various studies with that of present study. The present study shows normal study to be the commonest endoscopic finding 38%.Scalloping of duodenal folds was seen in 33.3% cases especially in cases of celiac disease.

Studies of Pipalya et al[19] revealed scalloping of duodenal folds to be the most common endoscopic finding. Study of Oregan et al reveals white spots along the course of duodenum to be the endoscopic finding in case of intestinal lymphangiectasia. In the present study endoscopic finding in intestinal lymphangiectasia is the mucosal oedema. In the present study some endoscopic findings other than the above mentioned were also present such as duodenal erosion (9.3%), mucosal oedema (5%), and duodenal ulcer (1.3%).

The present study shows villous atrophy in 15 cases, crypt hyperplasia in 9 cases and increase in IELs in a total of 24 cases. The present study matches with the studies of Balasubramanian P et al[15] and Pipalya et al[19] and Devi et al[20].
The present study shows celiac disease with Modified Marsh grade 3 to be the commonest finding followed by Modified Marsh grade 1. The present study matches with the study done by Daleep K et al[21].The present study also reveals two cases diagnosed as celiac disease on the basis of serological analysis without any morphological features suggestive of celiac disease. These cases were classified according to the Modified Marsh classification as grade 0.

The above table shows the comparison of the final diagnosis on duodenal biopsy in the patients presenting with the symptoms of malabsorption. The present study shows the most common diagnosis to be celiac disease proven histomorphologically as well as serologically. The present study matches with the study of Balasubramanian P et al[15] where celiac disease was the commonest diagnosis 38 cases. However, the present study does not match with

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Studies done by Devi et al[20] and Mahadev S et al[19] which reveals that the most common diagnosis to be chronic duodenitis 48 and 55 cases respectively.
On comparing with respect to Intraepithelial lymphocytosis the present study shows 16 cases of intraepithelial lymphocytosis. The present study matches with the study done by Mahadev S et al[19] and Devi et al[20] having number of cases of intraepithelial lymphocytosis to be 14 and 11 respectively. On comparing with respect to Giardiasis the present study shows 3 cases which matches with the study of Balasubramanian P et al[15][2 cases] and Mahadev S et al [19] [3 cases].The other causes in the present study includes Intestinal lymphangiectasia, Tubulovillous adenoma 1 case, duodenopathy 3 cases and many of the cases were within the normal limits.

Conclusion

Spectrum of duodenal biopsies in patients presenting with malabsorption symptoms may include a number of diseases which have similar presenting complaints. It may sometimes be difficult for clinicians to reach a diagnosis because of the overlapping presentations and laboratory parameters.
Duodenal biopsy plays and important role in reaching a diagnosis in cases of malabsorption as 45.2% showing abnormal endoscopic and laboratory findings in the form of villous atrophy, increase IEL's and features of duodenitis. Serological evidence in few cases of celiac disease showed good correlation especially with the higher MMO grade. Parasitic infection though having high incidence in Indian scenario formed a paltry sum (4%) in our study. It was finally concluded that a constellation of endoscopic, serologic, microbiologic and hematologic parameters is essential in patients with malabsorption to reach a final diagnosis.

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