Original Research Article

Upper Gastrointestinal Endoscopic Findings in Patients with Vitamin B12 Deficiency

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Abstract

Background: Vitamin B12 (Cobalamin) deficiency occurs in 3-40% of adult population. Stomach plays an important role both in absorption as well as in B12 deficiency. However, there is less emphasis on gastric endoscopic & biopsy changes in patients with B12 deficiency.
Aim and objective: To study gastric endoscopic and histopathology changes in patients with proven vitamin B12 deficiency.
Materials and methods: 75 patients with proven vitamin B12 deficiency were taken for the study. Detailed demographic data with presenting complaints, diet and alcohol history with detailed physical examination, including nervous system, were noted. Complete blood count, peripheral smear study, liver function tests, serum vitamin B12 and anti-intrinsic factor antibody (AIFA) were sent. Vitamin B12 deficiency is defined as levels < 200 pg/ml. All 75 patients underwent upper gastrointestinal endoscopy with gastric antral and corporal biopsies. The results were analyzed using SPSS version18.
Results: 44 patients (58.6%) were males, with mean age of 37.18 ± 14.8 years and 31 (41.4%) were females with mean age of 33.84 ± 19.7 years. The most common symptoms were generalized weakness (n=50, 66.7%), anorexia (n=45, 60%) and breathlessness (n=30, 40%) and the common physical findings included pallor (n=75, 100%), knuckle hyperpigmentation (n=33, 44%) and hepatomegaly (n=28, 37.3%). AIFA was found positive in 9 (12%) patients with B12 deficiency. Mean Hb, MCV, total leucocyte count (TLC) & platelet count (PC) were 6.14g% ±2.18 g% (range 1.7 – 11.2), 111.37 fL ±13.9 (range 64.9-134) and 4941.3 ± 2099.75 cells/cu.mm (range 1500-10000) and 1.29 ± 0.69 cells/cu.mm (range 0.09-3.20) respectively. The mean serum B12 levels were 125.94

pg/ml±56.96 (range 30-210). There was statistically significant difference of mean of MCV, TLC and platelet count among AIFA positive and negative cases ($p<0.05$). Upper gastrointestinal endoscopy was normal in 46 (61.3%), gastritis was noted in 17 (22.6%), and atrophy in 12 (16%) patients. Gastric biopsy showed chronic gastritis in 53 cases (70.6%), atrophic gastritis in 16 (21.3%), and normal in 6 (8%). There was no statistical difference observed between different levels of vitamin B12 with endoscopic findings and different levels of vitamin B12 with gastric biopsy reports. There was a very high statistical difference observed between different levels of age with endoscopy, with atrophy being most commonly observed in older age group.

Conclusion: Gastric endoscopic and histopathology changes in commonly seen vitamin B12 deficiency have received less emphasis in literature. In our study majority of B12 deficiency patients had normal endoscopy, followed by gastritis and atrophy. Histopathology showed majority as having chronic gastritis, followed by atrophic gastritis and a normal histology. Limitations of the study included small numbers of patients with the not so uncommon condition of B12 deficiency and lack of correlation between the endoscopic and biopsy findings.

Key words

Upper Gastrointestinal Endoscopy, Vitamin B12 Deficiency, Histopathology.

Introduction

Vitamin B12 (Cobalamin) deficiency ranges from 3-40% in adult population [1, 2]. Symptoms of B12 deficiency may vary from being asymptomatic to a wide variety of hematological and/ or neuropsychiatric manifestations. Stomach plays an important role both in B12 absorption and in B12 deficiency. Pernicious anemia (autoimmune gastritis) is one of the important cause for B12 deficiency. There is less emphasis on the endoscopic and histopathology features of the stomach in patients with B12 deficiency. Hence this study has been taken for evaluation of gastric endoscopy and biopsy features in patients with known vitamin B12 deficiency.

Aim and objectives

- To study endoscopic changes in the stomach with histopathology in patients with proven vitamin B12 deficiency.

Materials and methods

This was a prospective study done over a period of 2 years from December 2015 to December 2017. Prior Institutional Ethics Committee (IEC) approval was obtained for the research study. Written consent from the patients for the study entry and for endoscopy with gastric biopsy was obtained. A total of 75 patients, both in-patients and out-patients at a tertiary care hospital, with known vitamin B12 deficiency were selected for upper GI endoscopy. Detailed demographic data of the patients with presenting complaints including symptoms due to anemia such as general weakness, breathlessness, palpitations, giddiness, syncopal attacks, anorexia, bilateral lower limb swelling, jaundice and neuropsychiatric manifestations such as altered gait, imbalance, tingling and numbness and cognitive disturbances were taken. Dietary history (by 24 hours recall method) and alcohol history was taken. Significant alcohol intake was defined as intake more or equal to 60-80 g/day for 10 years or longer in men and more or equal to 20 g/day in women [3]. Patients were examined for the presence of pallor, icterus, lower limb edema, cheilosis, cheilitis, oral ulcers, bald tongue, lymph node enlargement (LNE), knuckle hyperpigmentation, hepatosplenomegaly. A detailed neurological examination was also done.

Investigations included complete blood count (CBC) with red cell indices, peripheral smear study, liver function tests, serum vitamin B12 level and anti-intrinsic factor antibody (AIFA).

Normal serum B12 level varies between 211-911 pg/ml, deficiency is defined as levels <200 pg/ ml [4]. Pernicious anemia is said to be present when AIFA were elevated (AIFA B>1.1 units, sensitivity 50% and specificity 100%) [5]. Patients below 15 years, obvious GI bleed or with known gastroduodenal malignancies were excluded from the study.

Patients were then taken for upper gastrointestinal (UGI) endoscopy. Endoscopy was performed by single gastroenterologist with an experience of 8 years in the field. The scope used was Olympus Actera Gastrointestinal Videoscope GI-Q150 series. Endoscopic findings were carefully noted and 2 gastric biopsies were taken, each from body (corpus) and antrum. Endoscopic findings included normal appearance of the stomach, atrophy and gastritis. Gastritis on endoscopy was defined as the presence of erosions or hemorrhage. Erosions were seen as breaks in the mucosa manifesting as multiple lesions with white bases that are commonly encircled by a halo of erythema (**Figure - 1**). Atrophy on endoscopy is defined as the disappearance of gastric rugae and thinning of the gastric mucosal folds with the prominence of blood vessels seen through the thin mucosa (paper money appearance) (**Figure - 2**) [6]. Erosive gastritis and friable mucosa are suggestive of gastritis on endoscopy.

Figure - 1: Gastric endoscopy showing normal fundus.

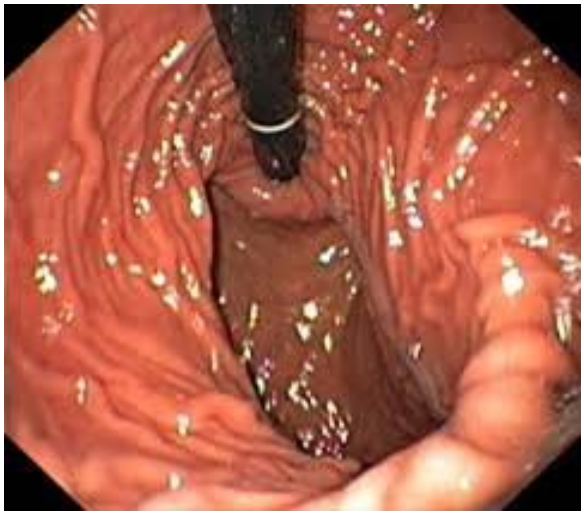


Figure - 2: Erosive gastritis.

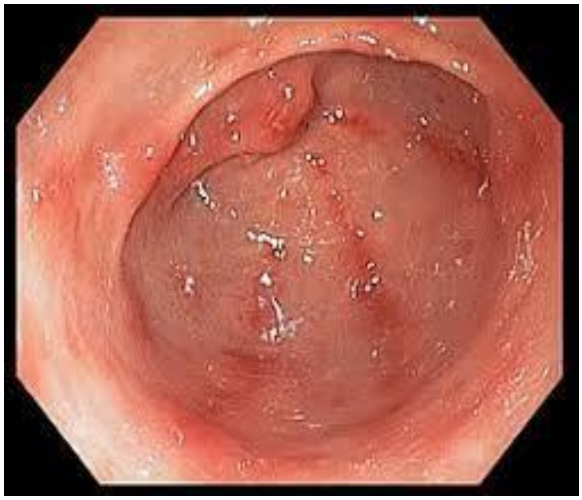


Figure - 3: Gastric atrophy.

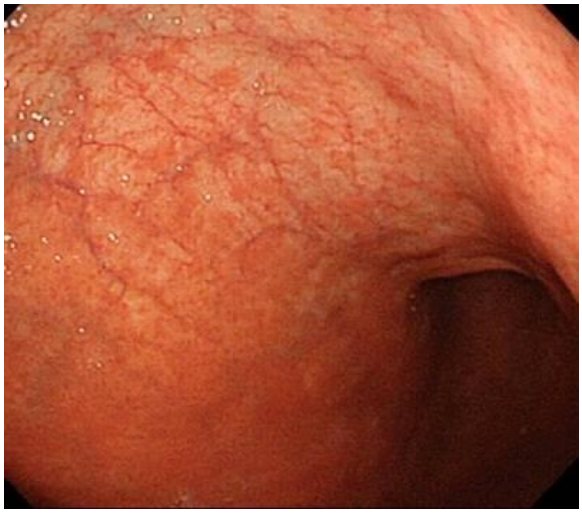
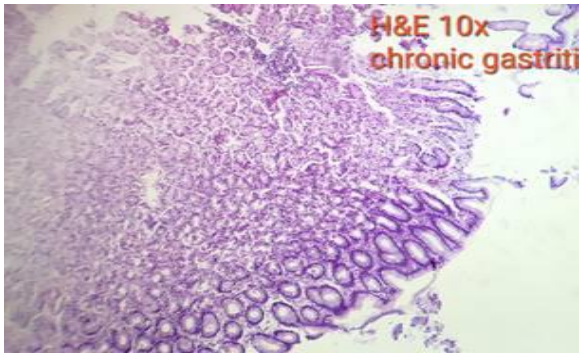


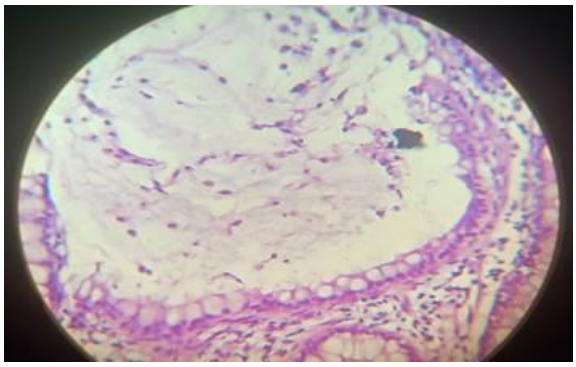
Figure - 4: Chronic gastritis.



The biopsy findings are classified as chronic gastritis, atrophic gastritis and gastric atrophy (**Figure – 3**). Chronic gastritis is defined as inflammation limited to the foveolar region unaccompanied by glandular atrophy (**Figure - 4**). Atrophic gastritis (**Figure - 5**) is defined as more extensive inflammation accompanied by

glandular atrophy and gastric atrophy is defined as thinning of the mucosa with an absence of inflammatory changes [7].

Figure - 5: Atrophic gastritis.



Statistical Analysis

The results were analyzed using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA). Results on continuous measurements were presented on mean±SD (min=max) and results on categorical measurements were presented in number (%). Normality of data was assessed using Shapiro-Wilk Test, Mann-Whiteny U-Test, Chi-square test with Yates correction was used to find out the significant difference between the groups. Spearmens correlation was used to find out the relationship between the variables. Significance was assessed at 5%.

Results

A total of 75 patients with vitamin B12 deficiency were evaluated in the present study. Demographic characteristics of the patients was shown in **Table - 1**.

Study reveals that, there was statistically significant difference of age among males and females (P<0.05%). Females are more of younger age group as compared to males.

Table - 1: Age and sex wise distribution of cases.

Age group (Years)	Males		Females		Total	
	No.	%	No.	%	No.	%
15-20	04	9.1	11	35.5	15	20.0
21-30	16	36.4	09	29.0	25	35.3
31-40	10	22.7	01	3.2	11	14.7
41-50	06	13.6	03	9.7	09	12.0
>50	08	18.2	07	22.6	15	20.0
Total	44	100.0	31	100.0	75	100.0
Mean±SD	37.18±14.8		33.84±19.7		35.79±16.32	

χ^2 value 11.76; P=0.019, significant

Figure - 6: Clinical presentation wise distribution of cases.

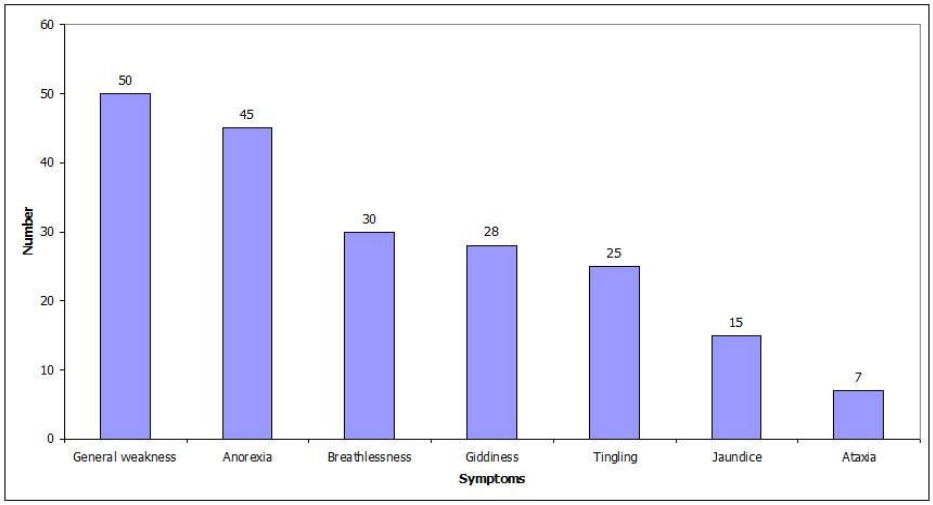


Table - 2: Clinical signs wise distribution.

Clinical signs	Frequency (n)	Percent
Pallor	75	100.0
Knuckle pigmentation	33	44.0
Hepatomegaly	28	37.3
Jaundice	17	22.7
Splenomegaly	15	20.0
Romberg's sign	7	9.3

Figure - 7: AIFA positivity and negativity.

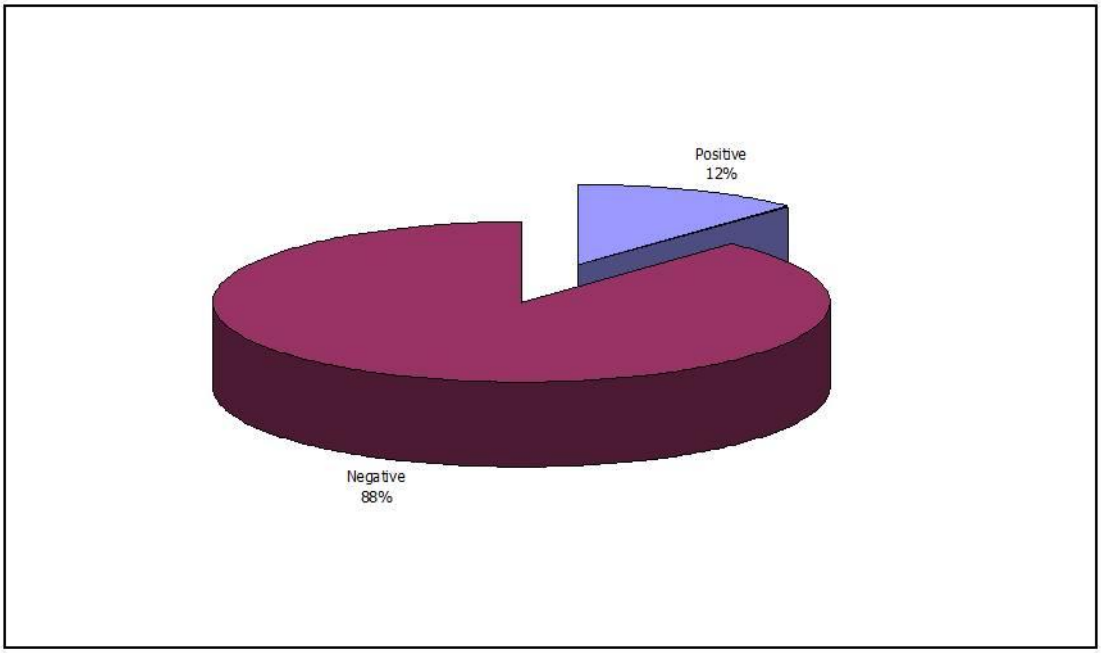


Table - 3: Mean Hb, MCV, TLC, Platelets, S. Cobalamin levels.

Variables	Mean±SD	Range
Hb (g%)	6.14±2.18	1.7-11.2
MCV	111.37±13.9	64.9-134.0
TC (in thousands)	4941.3±2099.75	1500-10000
PC (in lakhs)	1.29±0.69	0.09-3.2
Cbl (pg/ml)	125.94±56.96	30-210.0

Table - 4: Comparison of mean Hb (in g%), MCV (fL), TLC (in thousands), Platelets (in lakhs) and S. Cbl (pg/ml) with gender.

Variables	Mean±SD		Mann-Whitney V-value	p-value
	Males	Females		
Hb (g%)	6.40±2.27	5.77±2.03	576	0.26
MCV	110±12.39	113.33±15.81	557.5	0.18
WBC	4640.9±1963.4	5367.7±2242.67	558.5	0.18
Platelets (in lakhs)	1.26±0.69	1.33±0.70	639.5	0.65
Cbl (pg/ml)	129.8±54.25	120.35±61.07	630	0.57

Majority of the patients (n=57, 76%) were vegetarians, as compared to mixed diet (n=18, 24%). The most common symptoms were generalized weakness, present in 66.7% (n=50) followed by anorexia in 60% (n=45) and breathlessness in 40% (n=30) (**Figure - 6**).

Among the physical signs, pallor was universal in 100% (n=75), followed by knuckle hyperpigmentation in 44% (n=33) and hepatomegaly in 37.3% (n=28) (**Table - 2**).

Anti-intrinsic factor antibody (AIFA) was found positive in 12% (n=9) patients with vitamin B12 deficiency (**Figure - 7**).

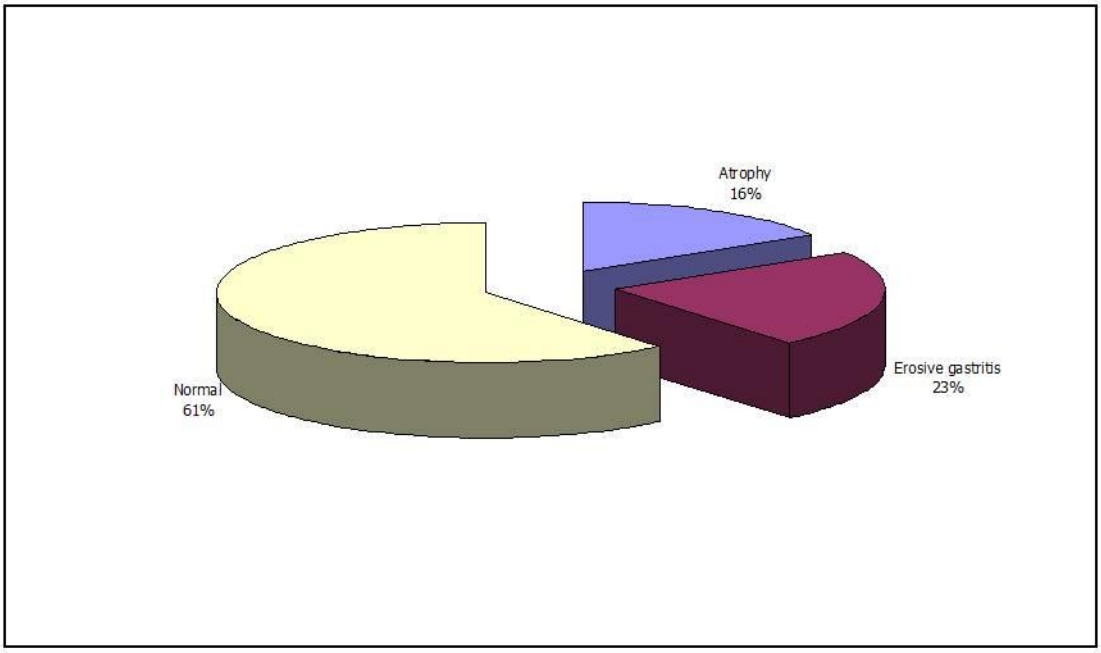
The mean Hb (in g%), MCV (in fL), total leucocyte (TLC) counts (in thousands), platelet counts (PC) (in lakhs) and serum cobalamin (Cbl) levels in (pg/ ml) are shown in **Table - 3**.

There was no statistical difference of means of Hb, MCV, TLC, platelets and CbL levels among males and females (p>0.05) (**Table - 4**).

Table - 5: Comparison of Mean Hb (g%), MCV, TLC, PC and Cbl (Pg/ml).

Variables	Mean±SD		Mann-Whitney V-value	p-value
	AIFA positive	AIFA negative		
Hb (g%)	5.53±2.14	6.23±2.19	257	0.51
MCV	128.20±4.59	109.08±13.15	38.5	0.001*
TLC	3555.56±1442.32	5130.3±2112.16	164.50	0.03*
Platelets (in lakhs)	0.83±0.51	1.35±0.69	169.5	0.04*
Cbl (pg/ml)	108.11±64.49	128.37±55.97	240	0.35

Figure - 8: Endoscopy wise distribution of cases.



There was a statistically significant difference of mean of MCV, TLC and platelet count among AIFA positive and negative cases (p<0.05). TLC and PC were significantly higher in AIFA negative cases as compared to AIFA positive cases, whereas mean MCV was statistically very highly significant in AIFA positive cases as compared to AIFA negative cases. There was no statistical significant difference of means of Hb and CbL among AIFA positive and negative cases (p>0.05) (**Table - 5**).

Figure - 9: Gastric biopsy wise distribution of cases.

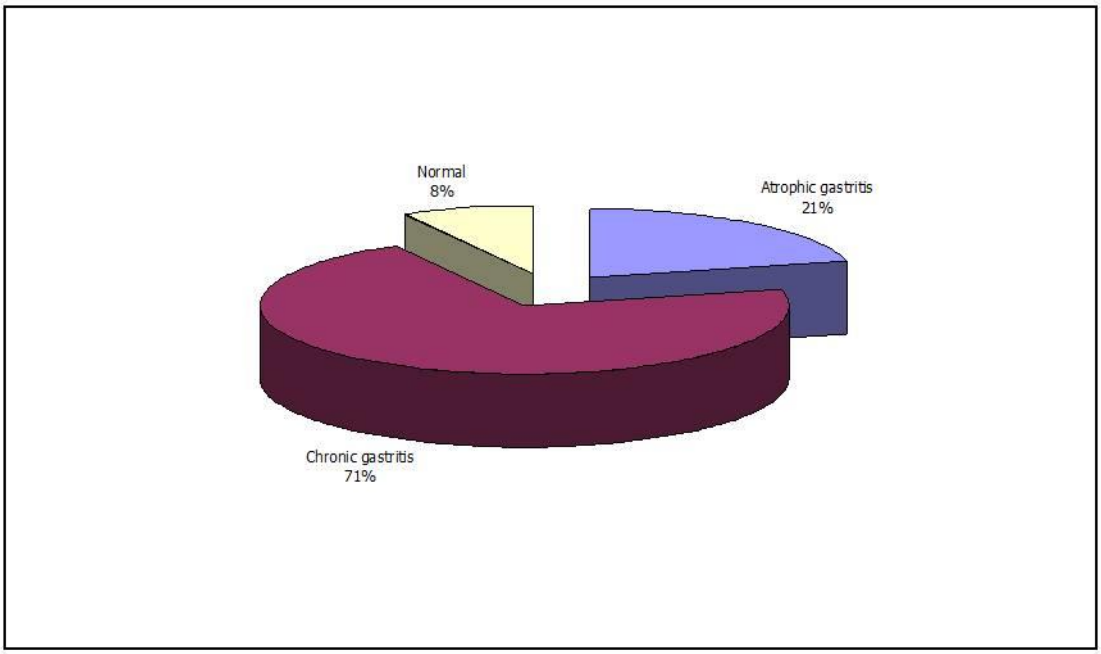


Table - 6: Comparison of cobalamin levels with endoscopy.

Endoscopy	Cobalamin		χ^2 value	p-value
	Up to 100	101-210		
Atrophy	7	5	5.268	0.07
Erosive gastritis	3	14		
Normal	15	31		
Total	25	50		

Table - 7: Comparison of cobalamin levels with gastric biopsy.

Gastric biopsy	Cobalamin		χ^2 value	p-value
	Up to 100	101-210		
Atrophic gastritis	08	08	4.48	0.11
Chronic gastritis	13	40		
Normal	04	02		
Total	25	50		

Table - 8: Comparison of Age with Endoscopy.

Endoscopy	Age group					χ^2 value	p-value
	15-20	21-30	31-40	41-50	>51		
Atrophy	01	01	00	01	09	28.27	0.0004*
Gastritis	00	07	05	02	03		
Normal	14	17	06	06	03		
Total	15	25	11	9	15		

Upper GI endoscopy was normal in 46 patients (61.3%), followed by gastritis in 17 cases (22.6%) and atrophy in 12 cases (16%) (**Figure - 8**).

Histopathology of gastric biopsy specimens showed chronic gastritis in 53 cases (70.6%), atrophic gastritis in 16 cases (21.3%), while the biopsy was normal in 6 cases (8%) (**Figure - 9**).

Table - 9: Comparison of age with gastric biopsy.

Gastric biopsy	Age group (Years)					χ^2 value	p-value
	15-20	21-30	31-40	41-50	>51		
Atrophic gastritis	01	01	01	02	05	10.96	0.20
Chronic gastritis	12	22	09	06	04		
Normal	02	02	01	01	00		
Total	15	25	11	09	15		

There was no statistical significance difference observed between different levels of cobalamin with endoscopic findings and different levels of cobalamin with gastric biopsy reports (**Table – 6, 7**).

There was a very high statistically significant difference observed between different levels of age with endoscopy, with atrophy being most commonly seen in older age group (**Table - 8**). Atrophy and gastritis cases were significantly more in higher age groups.

There was no statistical significant difference observed between different levels of age with gastric biopsy, although atrophic gastritis was more commonly seen in older age group (**Table – 9**).

Discussion

Gastritis is defined as inflammation of the gastric mucosa. Acute gastritis, which is characterized by dense infiltration of the stomach with neutrophilic leucocytes is rare. The more common is "active" gastritis, where neutrophils are present with chronic inflammatory cells (lymphocytes and plasma cells). Chronic gastritis is much more common than acute gastritis. It is mainly of three types (a) diffuse antral gastritis and chronic atrophic gastritis (or gastric atrophy) which is of two types (b) environmental metaplastic atrophic gastritis and (c) autoimmune metaplastic atrophic gastritis.

Diffuse antral gastritis is typically associated with *H.pylori* infection. Antral biopsy shows the gastric glands with neutrophil infiltration in addition to an increase in chronic inflammatory cells in the lamina propria.

Chronic atrophic gastritis (CAG) is of two types, namely environmental metaplastic atrophic gastritis (EMAG) also called multifocal atrophic gastritis and an autoimmune metaplastic atrophic gastritis (AMAG), also called diffuse corporal atrophic gastritis. EMAG is characterized by the involvement of both the gastric antrum and corpus with mucosal atrophy and intestinal metaplasia. Gastroscopy may show a pale mucosa, shiny surface and prominent submucosal vessels. The pathogenesis of EMAG is multifactorial, but H. pylori infection plays the most important role and has been incriminated in 85% of patients [8]. AMAG is an autoimmune destruction of glands in the corpus of the stomach. AMAG is the pathologic process in patients with pernicious anemia, an autoimmune disorder. These patients often have circulating antibodies to parietal cell antigens (most commonly proton pump – H^+, K^+-ATPase) and to intrinsic factor (IF). Many patients with AMAG have antibodies to *H.pylori* and/or *H.pylori* in their oxyntic mucosa. Thus, *H.pylori* may play a role in the early pathogenesis of AMAG [9]. Most clinical manifestations of AMAG result from the loss of parietal cells and chief cells of the oxyntic mucosa. Major effects include achlorhydria, hypergastrinemia, loss of pepsin and pepsinogens, vitamin B12 deficiency with megaloblastic anemia and increased risk of gastric neoplasms, particularly carcinoid tumours.

In our study, we included 75 patients with vitamin B12 deficiency and analyzed their endoscopic and gastric biopsy findings. There were 44 male (mean age with SD 37.18±14.8) and 31 female patients (mean age with SD 33.84±19.7). Majority of our patients were

vegetarians by diet. The clinical presentation was wide varied with general weakness and anorexia being most common symptoms (66.7% and 60% respectively). Other symptoms included breathlessness, giddiness, tingling sensation, jaundice and ataxia. Pallor was seen in all patients (n=75, 100%). Other important physical findings included knuckle hyperpigmentation, hepatomegaly, jaundice, splenomegaly and Romberg's sign. Similar symptoms and physical findings was noted in a study by S. Apte, et al. [10].

Complete blood picture in the study group showed severe anemia (Hb-6.4 g%±2.17), thrombocytopenia (20%) and pancytopenia (34.6%). The mean MCV (fL) was 111.37±13.9 fL (range 64.9-134). The mean cobalamin levels in our study group was 125.94±56.58 pg/ml. Nafil H, et al. [11] in their study, analyzed 121 cases with vitamin B12 levels ≤200 pg/ ml. Pallor (97.5%) was predominant symptom, followed by cardiovascular signs (46%), digestive symptoms (34.7%) and neurological signs (17.3%). The blood count showed anemia (Hb: mean=6.9 g/dl), macrocythemia (MCV: mean=109 fL), leucopenia was noted in 35 patients (29%), thrombocytopenia in 34 patients (28%) and pancytopenia in 21 patients (17.3%). The average vitamin B12 was 72 pg/mL. These observations are similar to observations made in our study group. Out of 75 patients 9 (12%) patients were AIFA antibody positive. There was a statistically significant difference of mean of MCV, TLC and platelet count among AIFA positive and negative ($p<0.05$), as mentioned in the results. An upper GI endoscopy was done in all the 75 patients to study for endoscopic and gastric biopsy findings. Upper GI endoscopy was normal in 46 patients (61.3%), gastritis and gastric atrophy was seen in 17 (22.6%) and 12 (16%) patients respectively. In contrast, in the same study by Nafil H, et al. [11], gastritis was most common finding and was seen in 82.7% of study population. Histopathology of gastric biopsy (in our study) showed chronic gastritis in 53 cases (70.5%), atrophic gastritis in 16 cases (21.3%) and normal in 6 cases (8%). Dholakia KR, et al. [7] in their study, on gastric histopathology in older patients with vitamin B12 deficiency showed, normal endoscopic picture as the most common endoscopy finding (36.7%) and chronic gastritis (59.3%) being the most common biopsy findings. This finding is in accordance with our study. Although patients with vitamin B12 deficiency had a lower rate of gastritis than the control group, they had a notably high level of gastric atrophy [7].

Demirci U, et al. [12] studied endoscopic findings in 37 patients with vitamin B12 deficiency. 29.7% (n=11) of the patients had pangastritis. Four pangastritis patients had duodenitis and one had Forrest type-III duodenal ulcer. 35.1% patients had antral gastritis, no patients with antral gastritis had duodenal pathology. 3 patients with vitamin B12 deficiency had intestinal metaplasia (IM) and atrophic gastritis (AG), while 1 patient had stomach cancer. However, there was no statistical difference of the above endoscopic findings between patient and control group in the above study. Our study, however, did not have control group. To note, there was no statistical difference observed between different levels of cobalamin with endoscopic findings and different levels of cobalamin with gastric biopsy reports (**Table – 6, 7**). There was statistical difference observed between different levels of age with endoscopy with gastric atrophy being most commonly seen in older age group (**Table - 8**). On gastric biopsy, atrophic gastritis was commonly seen in older individuals, although there was no statistical significance noted between age groups with gastric biopsy.

Conclusion

In conclusion, the endoscopic findings in patients with B12 deficiency included a normal endoscopy, followed by gastritis and atrophy. Histopathology showed majority as having chronic gastritis, followed by atrophic gastritis and a normal histology. The present study has certain limitations. The number of patients studied was only 75, which is relatively low

when the prevalence of B12 is seen and there is also lack of correlation between the endoscopic and biopsy findings.

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