Journal of Advances in Medicine and Medical Research

33(4): 26-34, 2021; Article no.JAMMR.65602
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Gastrointestinal Tract Endoscopic Evaluation of Iron Deficiency Anemia Patients without Gastrointestinal Manifestations Tanta University Hospitals Experience

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Authors' contributions

All authors contributed equally to this work, read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i430831
Editor(s):
(1) Dr. Syed Faisal Zaidi, King Saud Bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia.
Reviewers:
(1) Ramadori Giuliano, University of Göttingen, Germany.
(2) Marcel Adler, Switzerland.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65602

Original Research Article

Received 15 December 2020
Accepted 20 February 2021
Published 08 March 2021

ABSTRACT

Aims: Endoscopic evaluation of symptomless IDA patients and related lesions.
Study Design: A Cross-sectional epidemiological study.
Place and Duration of Study: The hematology unit of the Internal medicine department in Tanta university hospital, the duration of the study was 6 months from 1 January to 31 June 2019.
Methodology: 100 consecutive patients with laboratory base diagnosis of IDA without GI symptoms were involved in the study and their clinical and biochemical variables were recorded. All patients underwent esophagogastroduodenoscopy (EGD) and colonoscopy. Endoscopic findings were documented as the presence/absence of bleeding-related lesions or other causes of IDA.
Results: Possible cause of anemia was found in 95% and bleeding related lesions were found in 70% of patients. Upper GIT lesions were found in 70% of patients with 42% bleeding related lesions. Lower GIT lesions were found in 33% of patients with 21% bleeding related lesions. On multivariable logistic regression: old age, low hemoglobin (HB), low serum ferritin, and positive fecal occult blood test (FOBT) were predictive factors for GIT lesions and cause of IDA.

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Conclusion: Clinical and biochemical markers can predict GI lesions on endoscopy in IDA patients without GI symptoms. A high proportion of upper GI involvement makes EGD an initial endoscopic procedure however, a colonoscopy should be done in old age, and when upper GI lesions don't correlate with the severity of IDA.

Keywords: Iron deficiency anemia; gastrointestinal lesions; gastrointestinal symptoms.

1. INTRODUCTION

Iron deficiency anemia (IDA) is considered when the hemoglobin level is less than 13 g/dl in men and 12 g/dl in women according to the world health organization (WHO) criteria [1].

IDA has been cited as the most common cause of anemia globally [2]. It is a common disorder that is associated with many serious diseases including malignancies, particularly in GIT [3]. While the most common cause of IDA in pre-menopausal women is menstrual blood loss [4]. Occult or gross bleeding from GIT lesions is a common cause of IDA in men and postmenopausal women [5].

2-5% of populations in the developed countries have IDA and it is the common cause of referral to gastroenterologists. Endoscopies are an effective way of evaluating anemia in the hospital setting [6].

Despite invasive procedures such as bidirectional endoscopy sometimes it is challenging to diagnose and find gastrointestinal tract source of IDA [3]. Complete endoscopic examination is recommended [7]. Despite this recommendation, only 30% to 50% of the patients who were diagnosed with IDA receive endoscopic examination within 4 months [8].

About 10% of upper gastrointestinal tract endoscopy and colonoscopy were done for investigating IDA [9]. Endoscopy reveals a source of IDA in 30% to 50% of cases [3].

Asymptomatic patients represent a challenge as they may have a disease that can significantly progress over time [10]. So, IDA is considered a red flag for the possible presence of serious gastrointestinal tract disease because a substantial proportion of asymptomatic gastric cancer, colorectal cancer, and precancerous lesions may present with IDA [9].

In this study, we aimed to assess IDA patients without GI manifestations in Tanta University Hospitals GIT endoscopic evaluation.

2. MATERIALS AND METHODS

The study was a Cross-sectional, epidemiological study, carried out on 100 IDA patients admitted to the hematology unit of the Internal medicine department in Tanta university hospital, the duration of the study was 6 months from 1 January to 31 June 2019.

2.1 Inclusion Criteria

Patients newly discovered with IDA fit WHO criteria for diagnosis without GI manifestations.

2.2 Exclusion Criteria

Patients under the age of 18, Patients showing GI manifestations (dyspepsia, abdominal pain, colic, fresh bleeding per rectum, melena…etc.), chronic drug abusers (NSAID, steroids .etc.) and Females with menstrual cycle disturbances.

2.3 Methodology

All patients included in this study were subjected to detailed history taking including NSAID users, history of weight loss, and prior IDA therapy. General examination of the patients included (heart rate, blood pressure, pallor, jaundice….etc.) and abdominal examination for organomegaly or any other clinical finding.

The investigation done included complete blood count with differential, the iron profile including (S. ferritin, Transferrin saturation), CRP, fecal occult blood (when needed), H. pylori antigen in stool, Pelvi-abdominal ultrasound, upper gastrointestinal endoscopy, and colonoscopy in certain patients.

2.4 Statistical Analysis

Data analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** Qualitative data were described using the number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean,

standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The used tests were the Chi-square test, Fisher's Exact, and Odd ratio (OR).

3. RESULTS

3.1 Demographic Data

50% of studied populations were male versus 50% female, age from 18-40 years old were 22% and from 40-60 years old were 56% and > 60 years old were 22% with a mean age of 49.06 ± 15.35.

3.2 Laboratory Data

Hemoglobin level (Hb) was ranged from 4.6-11gm\dl with mean ± SD equal 7.73 ± 1.22 gm\dl. 2% of studied patients have mild anemia (10-12 gm/dl) while 45% of them have moderate anemia (7-10 gm/dl) meanwhile 53% have severe anemia (<7gm/dl).

Regarding iron studies, serum ferritin was ranged from 1.5-70.8 ng/dl with mean ± SD equal 17.51±12.72 ng/dl, transferrin saturation ranged from 2.5-21% with mean ± SD equal 9.07±3.89% while the total iron-binding capacity was 125-555 ug/dl with mean ± SD equal 349.3±102.7 ug/dl and the serum iron was 10 - 85 ug/dl with mean ± SD equal 23.56±16.04 ug/dl and all these results match with references for the diagnosis of IDA and confirm the diagnosis (Table 1).

3.3 Endoscopic Findings

Bleeding lesions detected during endoscopy in 70% of studied Patients, non-bleeding lesions in 25% while no lesions detected in 5%.

As regard to the distribution of lesions, 27% of lesions were founded in the colon, 28% were founded in the stomach, 21% were in the duodenum, 17% were in the esophagus and only 2% were founded in the ileum (Fig. 1).

The most common lesion detected during colonoscopy was cancer colon while the least common was A.V malformation, while in the upper gut esophageal varices were the commonest and celiac disease was the least common (Table 2).

According to Univariate analysis of Clinical and biochemical factors related to bleeding lesions on endoscopy: age >40 years old, Hb <9 gm/dl, MCV <70 Fl, serum ferritin <30 ng/ml, serum iron <30 ug/dl, TSAT <15% , TIBC >300 ug/dl and positive fecal occult blood test were predictors of the presence of lesions on endoscopy (Table 3).

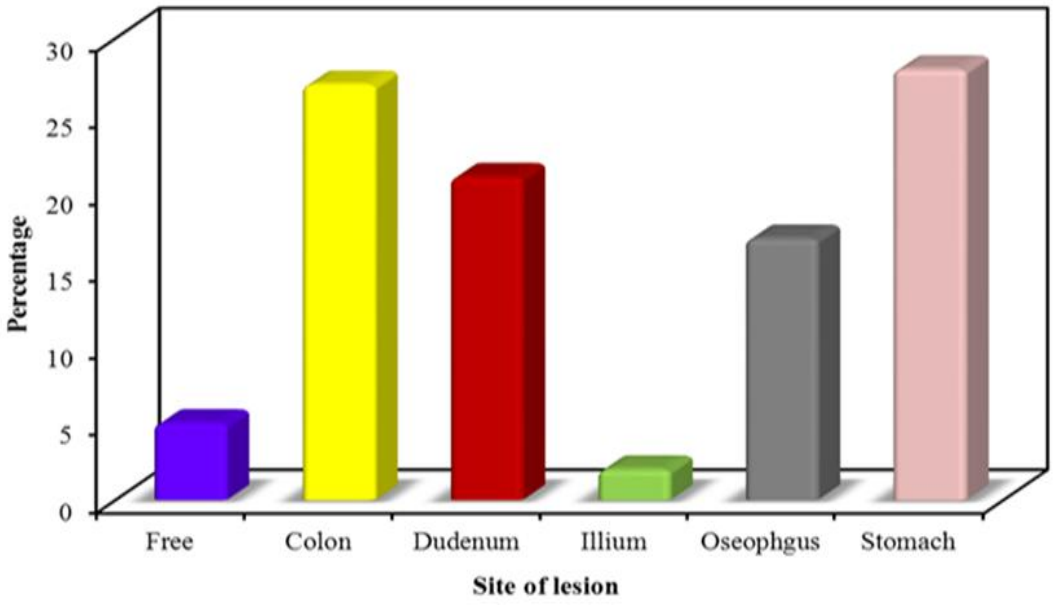

Fig. 1. Distribution of lesions according to their anatomical site

Table 1. Demographic data of the studied patients

Parameters		No (%)
●	**Age (years)**	
-	18 – 40	22(22%)
-	40 – 60	56(56%)
-	>60	22(22%)
●	**Sex**	
-	Male	50(50%)
-	Female	50(50%)
●	**Severity of anemia**	
-	Mild	2(2%)
-	Moderate	45(45%)
-	Sever	53(53%)
●	**FOCT**	66(66%)
●	**H pylori**	43(43%)
●	**HCV**	11(11%)
●	**Pelvi-abdominal U.S**	
-	**Normal**	**79(79%)**
-	**Abnormal**	**21(21%)**
-	Splenomegaly	12(12%)
-	Cirrhotic liver	16(16%)
-	Nephropathy	9(9%)
-	Congested liver	1(1%)
●	**Upper endoscopy**	
-	Free	30(30%)
-	Positive	70(100%)
●	**Lower endoscopy**	
-	Not done	31(31%)
-	Free	36(36%)
-	Positive	33(33%)
●	**Lesions**	5(5%)
Free	**Total number of lesions**	95(95.0%)
-	Upper only	62(62.0%)
-	Lower only	25(25.0%)
-	Upper + Lower	8(8.0%)
●	**Bleeding**	
-	No lesion	5(5%)
-	Non-bleeding	25(25%)
-	Bleeding	70(70%)
-	Upper only	42(60%)
-	Lower only	21(30%)
-	Upper and lower	7(7%)
●	**Number of lesions**	
-	One	83(87.4%)
-	Two	6(6.3%)
-	Three	5(5.3%)
-	Four	1(1.1%)

Table 2. Endoscopic findings and their relation to severity of anemia

Lesions	Total	Severity		
		Mild	Moderate	Severe
▪ **Non-lesion**	5 (5%)	-	-	-
▪ **Lesion**	95 (95%)	2(2%)	45(45%)	48(48%)
▪ Cancer Colon (One case caecum and other lt sided)	14 (14%)	–	6(6%)	8(8%)
▪ Esophageal varices	13 (13%)	1(1%)	7(7%)	5(5%)
▪ Gastritis (antral and pan gastritis)	13 (13%)	–	2(2%)	11(11%)
▪ Duodenitis	12 (12%)	–	5(5%)	7(7%)
▪ Gastric ulcer	12 (12%)	–	5(5%)	7(7%)
▪ Duodenal ulcer	9 (9%)	–	6(6%)	3(3%)
▪ Hiatal hernia	8 (8%)	–	2(2%)	6(6%)
▪ Internal piles	8 (8%)	–	4(4%)	4(4%)
▪ Esophagitis	5 (5%)	–	4(4%)	1(1%)
▪ Fundal varices	2 (2%)	–	1(1%)	1(1%)
▪ Portal hypertensive gastropathy	3 (3%)	–	2(2%)	1(1%)
▪ Ulcerative colitis	3 (3%)	–	2(2%)	1(1%)
▪ Nonspecific colitis	3 (3%)	1(1%)	2(2%)	–
▪ Gastric polyp	2 (2%)	–	–	2(2%)
▪ Crohn′ s disease	2 (2%)	–	2(2%)	–
▪ Ileitis	2 (2%)	–	–	2(2%)
▪ Celiac disease	1 (1%)	–	–	1(1%)
▪ Inflammatory Bowel Disease	1 (1%)	–	1(1%)	–
▪ Arterial -venous malformation	1 (1%)	–	–	1(1%)

Table 3. Univariate analysis of clinical and biochemical factors related to bleeding lesions on endoscopy

	Non-lesion (n =5)	Lesion (n = 95)	OR	95%CI	P-value
	No.(%)	No.(%)			
Age (years)					
<40	4 (80%)	18(18.9%)	17.111	1.8 -162.4	0.013*
≥40	1 (20%)	77(81.1%)			
Sex					
Male	3 (60%)	47 (49.5%)	1.532	0.25 - 9.59	0.648
Female	2 (40%)	48 (50.5%)			
Weight loss	1 (20%)	9 (9.5%)	0.419	0.04 -4.16	0.457
HB(gm/dl)					
≤9	2(40%)	86(90.5%)	14.333	2.11- 97.42	0.006*
>9	3(60%)	9(9.5%)			
MCV(Fl)					
≤70	2(40%)	86(90.5%)	14.333	2.11- 97.42	0.006*
>70	3(60%)	9(9.5%)			
Ferritin(ng/ml)					
≤30	2(40%)	83(87.4%)	10.375	1.57-68.59	0.015*
>30	3(60%)	12(12.6%)			
T.SAT (%)					
≤15	3(60%)	90(94.7%)	12	1.62-88.94	0.015*
>15	2(40%)	5(5.3%)			
TIBC (ug/dl)					
<300	4 (80%)	24(25.3%)	11.833	1.26-111.1	0.031*
≥300	1 (20%)	71(74.7%)			
Iron (ug/dl)					
≤30	1 (20%)	74(77.9%)	14.095	1.49-132.9	0.021*
>30	4 (80%)	21(22.1%)			
FOBT	0 0.0	64 67.4	–	–	0.002*

4. DISCUSSION

The previous study was included 100 GIT symptomless patients with IDA, who underwent endoscopic examination searching for the underlying cause of IDA. The majority of the studied population (95% of participants) have positive endoscopic findings (either in upper or lower or both endoscopies) similar to a study by Majid et al. [10].

In the study by Annibale et al. [11]. A likely cause of IDA in the gut was detected in 85% of patients out of 668 patients without GIT manifestations. Also, in Majid et al. [10] study, IDA gut cause could be detected in 71%.

In this cohort, the frequency of lesions involving the lower gastrointestinal tract was low as about only 35 lesions were founded in contrast to 79 lesions that were founded in upper GIT this was in agreement with Majid et al. [10] study but striking and in contrast to Wang et al. [12] study in which lower GI lesions were more or equal to upper GI tract lesions.

70% of participants had bleeding lesions while 25% had non-bleeding lesions related to or cause IDA, this agreed with Sabel'nikova et al. [13]. Those with non-bleeding lesions (H.PYLORI related gastritis and celiac disease) that can cause IDA. Therefore, previous study support taking biopsies (gastric and duodenal) during gastroscopy, which identified other common causes of iron deficiency anemia such as celiac disease, this agreed with Bampton et al. [14].

Results of previous studies have implicated Helicobacter pylori infection as a potential cause of IDA. Several theories have been put forward as to how H pylori infection can lead to IDA, including impairing iron absorption, competing with the host for the uptake of iron, or elevating the pH and reducing vitamin C concentration [15].

However, in a recent retrospective study by Daniel et al. [16], they found no evidence that H. pylori is involved in causing IDA. IDA is resolved in most subjects regardless of H pylori treatment status.

In the previous study, severe IDA occurred with certain lesions including colorectal cancer, gastritis, esophageal varices, gastric ulcer and duodenitis, the results of the study by Dunne et al. [17] were concomitant with the previous study.

Participants older than 60 years old, both upper GIT endoscopy and colonoscopy were equal in the identification of lesions while most of the autoimmune disorders such as celiac disease, Crohn′s disease, and ulcerative colitis were found in participants less than 40 years old in agreement with Zhu et al. [18], Annibale et al. [11], Short et al. [19], and in contrast with Majid et al. [10] who suggested that upper GIT endoscopy has superior value over colonoscopy in all age groups regardless the gender of patients.

Almost all of the premenopausal females have GI lesions more in upper GI than lower GI tract with increased risk of GIT malignancy suggesting that GIT evaluation should be pursued in those who have severe anemia or remains refractory to iron treatment, have significant weight loss, positive fecal occult blood testing and those whose menstrual blood loss does not correlate with the severity of their IDA in contrast with Clark et al. [20] who suggested that IDA in most premenopausal women can be attributed to menstrual blood loss and insufficient dietary intake. While in agreement with our cohort Green et al. [21], reported that 111 women referred to GI specialists for IDA were associated with gastrointestinal lesions either in upper or lower GIT.

Bini et al. [22] conducted a study of 186 premenopausal women who referred for gastroenterological evaluation, with HB less than 10gm/dl, FOBT positivity, and weight loss where GIT lesions were found in almost all referral group.

In the previous study, upper GIT endoscopy findings were more frequent and less serious than colonoscopy findings and meanwhile colon cancer was the most common lesion in colonoscopy agreed with Abdel-Aty et al. [23].

An interesting finding in the previous study was many patients had either premalignant or malignant lesions about 14 (14%) participants had cancer colon without any complaint similarly to and in agreement with Stephen et al. [24] that ranges from 10-50% of patients with malignancy.

Previous results are consistent with other studies and support the need to evaluate the lower GIT in patients with IDA, especially those over the age of 50 years, even if a lesion is found at upper endoscopy [14].

However, Majid et al. [10] showed that a small number of patients had malignancies and this low prevalence of tumors could be explained by a low incidence of GIT malignancies in the Malaysian population [25].

Another interesting finding in the previous study was the finding of more than one lesion in the same participant as 6 patients had 2 lesions, 5 patients had 3 lesions while 1 patients had 4 lesions and this support the need to evaluate either upper or lower GI tract even if the lesion is found in one of them before the other [19]. That is why a bidirectional endoscopic evaluation is necessary for the workup of IDA.

In contrast with those study by Fireman et al. which recommend performing lower GIT endoscopy first [26]. In our work, 62% of participants had upper GIT involvement only versus 25% had colonic involvement only meanwhile lesions involving both tracts were present in 8 patients and so our study favors upper gastrointestinal tract evaluation first in agreement with Majid et al. [10] and Annibale et al. [11].

The predictors of endoscopic lesions in IDA patients without gastrointestinal symptoms were old age, low HB, low mean corpuscular volume, low serum ferritin, and positive fecal occult blood test in line with Majid et al. [10] and Annibale et al. [11].

The higher yield in our study is that our participants were obtained from patients referred to a hematology department with IDA while Previous studies investigated less homogeneous groups of patients, composed of both inpatients and outpatients who were referred for endoscopy because of iron deficiency anemia, fecal occult blood positivity, or both, Another explanation of the higher yield of our study is that most previous studies were conducted in older patients with a mean age ranging from 60 to 70 years [14], while our study has a lower median age but the lower median age of our sample could explain the lower prevalence of certain lesions, such as colonic polyps, which are common among older patients.

5. CONCLUSION

All IDA patients without GIT symptoms should undergo GIT endoscopic evaluation especially in men and postmenopausal women. All premenopausal women should undergo GIT endoscopic evaluation if anemia is severe, refractory, with weight loss, with positive FOBT, and if menstrual blood loss doesn't explain or correlate with the severity of IDA. Upper GIT endoscopy has the upper hand as the first procedure, but colonoscopy should be done in old age patients and if upper GIT lesion doesn't correlate with the severity of IDA.

CONSENT

Informed written consent was obtained from all patients after a full explanation of the benefits and risks of the study. Privacy of all patients' data is granted by a special code number for every patient file that includes all investigations.

ETHICAL APPROVAL

The protocol was approved by the local ethics committee to conduct this study and to use the facilities in the hospital. The study complied with the Declaration of Helsinki and ethical approval was obtained by the review board of the Faculty of Medicine, Tanta University (Approval Code: 32654/10/18).

ACKNOWLEDGEMENTS

This paper and the research behind it would not have been possible without the exceptional support of my supervisors (Drs. Mohamed El sayed Enaba, Amr Mouhamed Gawaly and Hossam Abd El mohsen Hodeib) for their knowledge and exacting attention to detail have been an inspiration and kept my work on track.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/65602