

## Role of Upper and Lower Gastrointestinal Endoscopy in Investigating the Etiologies of Iron Deficiency Anemia in Postmenopausal Women

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### ABSTRACT

#### Background:

Iron deficiency anemia has been considered as an alarming sign of the possible presence of malignancy in the digestive tract. Inadequate assessment of such affected patients can lead to delay in the diagnosis of gastrointestinal (GI) tumors especially colorectal cancers. Therefore the present study examined the upper and lower GI tract of postmenopausal women with iron deficiency anemia by GI endoscopy.

#### Materials and Methods:

Women aged over 45 years referred to Gastroenterology Clinic of Imam Khomeini Hospital were asked about their menstruation. Postmenopausal women with the anemia were enrolled. A list of laboratory studies were performed for all included patients. These laboratory studies included complete blood count (CBC), iron profile and stool examination for occult blood. 103 postmenopausal women with iron deficiency anemia according to laboratory tests were interviewed and their clinical and biochemical variables were recorded. All of the study patients underwent esophagogastroduodenoscopy and colonoscopy. The endoscopic findings were recorded regarding the presence of GI lesions causing iron deficiency anemia or the lack of them.

#### Results:

A total of 103 patients participated in this study. Endoscopy revealed a source of iron deficiency anemia in 90.3% of the study population. Upper and lower GI tract lesions were found in 73.8% and 51.5% of the patients, respectively. The most frequent lesions in the upper GI endoscopy were severe gastroesophageal reflux disease involving 34 patients (33%) followed by gastric erosions in 31 cases (30.1%) and duodenal ulcer in 15 cases (14.6%).

#### Conclusion:

In postmenopausal women with iron deficiency anemia as in men, it is necessary to examine the GI tract.

**Keywords:** Iron Deficiency Anemia; Gastrointestinal Lesions; Postmenopausal Women; Endoscopic Investigation.

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#### INTRODUCTION

Studies have estimated that 1.6 billion people worldwide (25%) have anemia. Of them 50% is due to iron deficiency anemia (1-4). Both in developing and developed countries, iron deficiency anemia is one of the most common nutritional deficiency anemias (5-7).

Unbalanced iron intake, malabsorption, blood loss, and altered iron demand situation such as pregnancy are the main causes of iron deficiency anemia (8-10). Iron deficiency anemia leads to inadequate production of erythrocytes and the morphology of red cells would change to microcytic and hypochromic cells (7,11) leading to their malfunction.

Some of the common and known etiologies for iron deficiency anemia include nutritional deficiency, parasitic infections, malabsorption, and some other diseases (12,13). Iron is absorbed in gastrointestinal (GI) tract like other crucial elements. Therefore any disease in this tract like blood loss and altered iron absorption can lead to iron deficiency (14,15). GI tract ulcers and carcinomas, atrophic gastritis, colonic adenoma, vascular ectasia, non-steroidal anti-inflammatory drugs, gastropathy or enteropathy, and portal hypertensive gastropathy or colopathy are the main sources of blood loss in GI tract.

Moreover there are some other conditions in GI tract that affect iron absorption including, inflammatory bowel disease, intestinal tuberculosis, cystic fibrosis, tropical sprue, celiac disease, *H. pylori* infection, and malignancies (14-16).

There are few published articles about the etiology of iron deficiency anemia in postmenopausal women but based on current investigations the main sources of iron deficiency anemia in postmenopausal women are GI blood loss and altered absorption (17,18). Hence, in the current study we evaluated the GI tract of postmenopausal women with iron deficiency anemia by upper and lower endoscopy to find the main sources of iron loss.

## MATERIALS AND METHODS

### Ethical Approval

All patients provided informed consent to participate in the study. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran.

### Patients

Patients were recruited from all public clinics of gastroenterology affiliated to Mazandaran University of Medical Sciences, Sari and private clinics of all collaborating colleagues. All women aged more than 45 years referred to collaborating gastroenterologists to evaluate the source of iron deficiency anemia were asked for their menstrual status. After ensuring the patient's menopausal status, and getting a written informed consent the evaluations were done.

Iron deficiency anemia was defined as hemoglobin (Hb) less than 12 g/dl with the following criteria: serum iron  $\leq$  45  $\mu$ g/dL, total iron binding capacity

(TIBC)  $>$  360  $\mu$ g/dL, transferrin saturation  $\leq$  20, and serum ferritin concentration  $<$  20  $\mu$ g/L.

Exclusion criteria were active bleeding (GI tract, menstrual, urinary), history of gastric or colon surgery, history of GI cancers, history of iron supplement therapy, coagulopathy disorders, current use of anti-coagulant agents, and those who refused to undergo upper and lower endoscopy.

The following lesions were defined as sources of iron deficiency anemia and were searched for in endoscopy of upper GI tract: Gastric ulcer and erosions, esophageal ulcers, duodenal ulcers and erosions, endoscopic signs of suspicious celiac disease, gastric carcinoma, watermelon stomach, erosive esophagitis, erosive gastritis, gastro-esophageal reflux disease (GERD) class C and D, gastric and duodenal adenocarcinoma, gastric and duodenal polyp, gastric mucosal infiltration, and gastric and duodenal vascular ectasia.

Celiac disease was proven by taking biopsy samples and atrophic gastritis was considered as a cause of iron deficiency anemia after ruling out the above reasons. Biopsy samples were taken from the second part of the duodenum when scalloping was seen on upper endoscopy and if the upper endoscopy and colonoscopy were normal.

The following lesions were considered as etiologies of iron deficiency anemia in colonoscopy: solitary rectal ulcer, colon polyps (adenoma), colon cancer, ulcerative colitis, Crohn's disease, internal hemorrhoids, and anal fissure with bleeding, idiopathic cecal ulcer, and vascular ectasia.

### Statistics

For statistical analysis, data were entered to MS Excel spread sheets. The procedures included transcription, preliminary data inspection, content analysis, and finally interpretation. Investigators used percentages to clarify epidemiological variables (SPSS software, version 22, Chicago, IL, USA). Univariate analysis and simple logistic regression were applied for independent variables.

## RESULT

The study population included 103 postmenopausal women with iron deficiency anemia who fulfilled the inclusion criteria. The mean  $\pm$  SD of age in these

**Table 1: Biochemical characteristics of patients in this study**

Parameters	Mean ± SD
Hb (g/dL)	10.27 ± 1.23
MCV (fL)	78.22 ± 5.09
RBC (million number)	3.84 ± 0.49
Platelet (thousand number)	294.28 ± 95.37
Serum iron (µg/dL)	29.79 ± 8.46
TIBC (µg/dL)	383.04 ± 61.51
Transferrin saturation (%)	7.98 ± 2.63
Ferritin (µg/dL)	13.30 ± 3.80
ESR (mm/h)	25.56 ± 1.76

TIBC: total iron binding capacity

**Table 2: Etiologies of iron deficiency anemia in upper endoscopy**

Endoscopic findings	Positive (number)	Positive (percent)
Gastroesophageal reflux	34	33
Erosive gastritis	31	30.1
Gastric ulcer	13	12.6
Gastric adenocarcinoma	6	5.82
Gastric polyps	4	3.9
Gastric vascular ectasia	5	4.9
Erosive duodenitis	4	3.9
Duodenal ulcer	15	14.6
Duodenal atrophy (scalloping)	2	1.9

**Table 3: Findings of colonoscopy in postmenopausal patients with iron deficiency anemia**

Endoscopic findings	Positive (number)	Positive (percent)
Anal fissure	2	1.9
Internal hemorrhoids	17	16.5
Ulcerative colitis	9	8.7
Crohn's disease	2	1.9
Vascular ectasia	1	1
Adenocarcinoma of colon	4	3.9
Polyp	11	10.7

patients were  $63.57 \pm 8.84$  ranging from 50 to 86 years. One patient had history of hysterectomy. Biochemical characteristics of the patients with iron deficiency anemia were summarized in table 1.

Transferrin saturation of less than 20% was defined as iron deficiency anemia, and all subjects in this research had low transferrin saturation level.

Considering the normal value for RBC count of 3.6 - 5.5 million/ $\mu$ L, 78 patients (75.7%) had normal

RBC counts. CRP was positive in 15 cases (14.6%) but less than 20  $\mu$ g/L (according to inclusion criteria), whereas 88 patients (85.4%) had negative result for CRP. Normal erythrocyte sedimentation rate (ESR) was defined as  $(age + 10)/2$  (19). 90 (87.4%) patients had normal ESR. Fecal occult blood test was positive in 24 patients (23.3%).

### Endoscopic findings

In 93 cases (90.3%) endoscopic/colonoscopic lesions were found but in 10 patients (9.7%), there were no reportable lesions both in upper and lower endoscopy (tables 2 and 3).

40 cases had only one lesion in upper endoscopy. In 17 cases lesions were found only in lower endoscopy and in 36 patients simultaneous lesions both in upper and lower GI tract were reported. Among these patients, two cases had celiac disease, which was approved by biopsy.

### Findings in upper endoscopy

Upper endoscopy revealed that 76 cases (73.8%) had at least one reason for bleeding. Severe GERD was reported in 34 cases of whom 32 cases had Los Angeles (LA) class C and 2 patients had LA class D.

Antral erosions were seen in 31 patients but distributions of gastric ulcers were as follows; one lesion in the cardia, one in the fundus, two lesions in the incisures, and eight lesions in the antrum. Gastric adenocarcinoma was detected in six subjects in which two were in the cardia, one case in the body, and three lesions in the antrum. Among five cases of ectasia, three lesions were observed in the fundus, and two lesions in the body. Four cases had gastric polyp with the following distribution; one in the cardia and three in the antrum (table 2).

### Findings in colonoscopy

50 (48.5%) patients had normal colonoscopy and 53 (51.5%) patients had at least one lesion in colonoscopy (table 3). Extension of ulcerative colitis lesions were as follows: three cases had extensive colitis, four cases had left sided colitis, whereas one patient had limited proctitis. The severity of the disease was divided to two cases with severe (both left sided) and six cases with mild activity (proctitis to extensive distribution).

**Table 4: Results of univariate analysis showing clinical and biochemical factors associated with reason in endoscopy**

Variables	Patients with one defined reason for anemia (n:93)	Patients with no defined reason for anemia (n:10)	P value
Age	63.68±8.90	62.50±8.65	0.296
Hb (g/dL)	10.18±1.23	11.15±0.71	0.033
Hb≤9 (g/dL)	18 (19.35%)	0 (0%)	0.098
MCV (fL)	78.17±5.31	78.69±2.35	0.739
MCV≤60 fL	1 (1.07%)	0 (0%)	1.000
ESR (mm/h)	24.16±14.31	37.27±34.04	0.103
Serum iron (µg/dL)	29.47±8.56	32.80±7.06	0.138
Serum iron≤10 (µg/dL)	0 (0%)	0 (0%)	0
TIBC (µg/dL)	383.53±64.06	378.50±30.06	0.084
Transferrin saturation (%)	7.91±2.71	8.63±1.71	0.110
Ferritin µg/L	13.11±3.87	15.10±2.71	0.915
Ferritin≤5 µg/L	1 (1.07%)	0 (0%)	1.000
(Positive) FOBT	24 (25.80%)	0 (0%)	0.997

Hb: hemoglobin; MCV: mean corpuscular volume; ESR: erythrocyte sedimentation rate; TIBC: total iron binding capacity

Two cases had Crohn's disease up to descending colon, which were not severe. Among 11 observed polyps; one was in the ascending colon, one in the rectum, and nine in the sigmoid. Eight polyps were pedunculated and three were sessile. Pathological study showed that two were hyperplastic, three were villo-tubular, and others were undefined.

The mean ± SD of polyp size was 7.45 ± 2.65 mm and all of them were less than one cm. Adenocarcinoma was seen in four cases, three in the ascending colon and cecum, and one in the descending colon.

Results of univariate analysis (table 4) has revealed that Hb level ( $p = 0.026$ ) and ESR ( $p = 0.037$ ) had significant correlation with the chance of finding a bleeding lesions. For both bleeding and non-bleeding lesions only Hb had significant association ( $p = 0.033$ ).

## DISCUSSION

In the current study, we investigated the etiologies of iron deficiency anemia in postmenopausal women. A total of 103 patients participated in this study. Endoscopy revealed a source of iron deficiency anemia in 90.3% of cases. Upper and lower GI tract lesions were found in 73.8% and 51.5% of the participants, respectively. The most common lesions in the upper GI endoscopy were peptic disorders including GERD, which affected 33% of the patients, followed by gastric erosions in 31 cases (30.1%). Internal hemorrhoids

were observed in 17 cases (16.5%), which were the most frequent lesions in the lower GI endoscopy.

Of utmost importance was the finding of malignant diseases (gastric cancer and colon cancer) in nearly 10% of cases. These patients did not complaint of relevant symptoms and were found asymptomatic, making the endoscopic evaluation in postmenopausal women suffering from iron deficiency anemia cost effective.

The finding of inflammatory bowel disease was also interesting in these cases with no direct complaints in that regard, however retrospectively some patients when asked directly and concisely reported some mild changes in their bowel movement, which was considered by themselves as normal or age-dependent or due to diet changes because the symptoms had occurred slowly over a longtime. We have also found extensive colitis and severe forms in this case series, showing the importance of iron deficiency anemia as indicators of inflammatory bowel disease in this subset of patients.

A major issue in this study is that these findings in upper and lower GI endoscopy do not necessarily mean that these findings are the cause of iron deficiency anemia. To document bleeding from a lesion active bleeding/oozing from the lesion is necessary, which is not possible in most cases, even in the presence of active bleedings. In other words in this study the

association of endoscopic findings has been reported and causality cannot be proven precisely.

Despite the current investigations, we found no sources for iron loss in 10 patients (9.7%), which indicates that some other methods must be considered for the diagnosis of these series. In this regards, Lucas and colleagues (21) reported that the main etiology of iron loss in some cases were undetectable.

Majid Shahid and his colleagues (22) examined 95 patients with anemia and revealed a source of iron loss in 71% of the study population in which 53% were bleeding lesions. Among these cases 61% had upper lesions and 10% had lower lesions.

In a recent clinical trial by Khansa Qamar and co-workers (23) malabsorption of iron was one of the causes of iron deficiency anemia in postmenopausal women. They revealed that the frequency of iron malabsorption in postmenopausal women was 6.8%.

Goddard and colleagues have shown that the prevalence of malabsorption in iron deficiency anemia is about 5 - 10%. In their research the most common etiology was celiac disease (24). In this regards, Vannella and co-workers have reported that bleeding lesions as a source of iron loss were more common in elderly objects in comparison with young patients (25).

Some researchers reported anemia in chronic diseases with co-existing iron deficiency (26-30). Anemia in chronic diseases can be defined as high level of CRP, decreased transferrin saturation (< 20%), normal serum ferritin (30 - 100 ng/mL), and high level of serum soluble transferrin receptor (sTfR)/log ferritin ratio (> 2). Herein, Pasricha and co-workers also have reported that anemia with chronic diseases with co-existing iron deficiency is more frequent in old patients (26). In our study, 15 cases (14.6%) had positive CRP test but in 88 patients (85.4%) CRP was negative. ESR was normal in 90 (87.4%) patients and 13 cases (12.6%) had high level of ESR.

In our study, 9.7% of the patients had no GI findings, which was close to other reports. Luman and colleagues (31) reported that frequency as 10% and in Dalamia's (32) study, it was 8.6%. But some other studies revealed more frequency of GI signs or symptoms including the studies by Niv (29%) (33), Patterson (66%) (34), Majid Shahid (29%) and their colleagues. These differences might be due to the

sample sizes, age of participants, ethnic backgrounds, and others. Moreover, in the study by Patterson and colleagues (34) about 25% of the cases refused to participate in colonoscopy.

Niv and coworkers (33) reported that 29% of postmenopausal women with iron deficiency anemia had colon cancer. Patterson reported the frequency as 10% (34). In the current investigation 27% of cases had polyp or malignancy in GI tract.

One of the limitations of this study was that we did not examine the small intestine. Some sources of iron deficiency anemia are in ileum and jejunum and future investigations should consider this part of GI tract in their evaluations. These include three categories: 1. Premucosal causes (chronic pancreatitis, cystic fibrosis, Zollinger-Ellison syndrome, etc.) 2. Mucosal causes (tropical sprue, Whipple's disease, amyloidosis, etc.) 3. Postmucosal causes (intestinal lymphangiectasia, malignant lymphoma, macroglobulinemia, etc.) (35).

Moreover, an important point of the current research was that in the evaluation of iron deficiency anemia in postmenopausal women, gastroenterologists should consider all causes of anemia similar to men. Although management of anemia in many postmenopausal women is similar to premenopausal women, we advise this is wrong and all cases should be handled as men.

## CONCLUSION

Our study showed that the benign lesions of upper and lower GI tract are more common in postmenopausal women with iron deficiency anemia, however malignant lesions do occur in a reasonably high percentage of these patients. Due to high rates of morbidity and mortality of such GI tract disorders, the importance of evaluations of postmenopausal women with iron deficiency anemia cannot be overlooked. So it can be concluded that in postmenopausal women with iron deficiency anemia, like men endoscopic GI tracts evaluation, is required.

## Limitations

Selection of cases was based on referral of postmenopausal women having iron deficiency anemia on their routine laboratory studies. A complete history of gastrointestinal symptoms was not available. It

could be said that the study population have been referred because of their associated GI symptoms and do not represent all postmenopausal women with iron deficiency anemia.

### CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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