

Gastrointestinal symptoms are closely associated with depression in iron deficiency anemia: a comparative study

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BACKGROUND AND OBJECTIVES: Until now, very few studies evaluated the association between gastrointestinal and psychiatric symptoms in iron deficiency anemia (IDA). The study investigated the frequency of functional dyspepsia (FD) in IDA patients and determined its association with depression and somatization.

DESIGN AND SETTINGS: The study was conducted at the Hematology Department of Trakya University Medical Faculty, which is a tertiary referral center in northwestern Turkey. It was a case-control study.

MATERIALS AND METHODS: A total of 125 consecutive IDA patients and 57 healthy control subjects were included. Patients and controls were questioned about the severity of their gastrointestinal system (GIS)-related symptoms and the presence of constipation and associated symptoms using a visual analog scale. In addition, IDA patients were administered a validated depression scale (Beck Depression Inventory, BDI) and somatization symptoms checklist.

RESULTS: IDA patients had more frequent self-reported constipation compared with controls (56% vs 22.8%, $P < .001$). The mean scores of bloating, dyspepsia, and constipation-related quality of life (QoL) disturbance were significantly higher in the IDA group than in the control group (all P values $\leq .01$). A total of 71 IDA patients were depressed according to the BDI. Depressed IDA patients had higher mean reflux, bloating, halitosis, and dyspepsia-related QoL disturbance scores compared with nondepressed patients (all P values $\leq .01$). Their frequency of self-reported constipation and mean constipation-related QoL disturbance score (P values, .002 and $< .001$) were also higher. Depressed IDA patients had significantly higher somatization scores compared with others ($P = .001$).

CONCLUSION: An increased frequency of dyspepsia symptoms and constipation-related QoL disturbance were observed in IDA patients. The findings of this study suggested that in IDA patients without red flags in favor of malignancy, physicians should try to uncover any psychiatric factors before undertaking extensive GIS investigation.

Iron deficiency anemia (IDA) is common in the general population, and the investigation for causes for blood loss are quite important.¹ In addition to investigation for the cause of menstrual blood loss, the investigation of the gastrointestinal system (GIS) also has utmost importance to reveal the etiology of IDA. The questioning of GIS symptoms and interrogation of alerting symptoms help the clinician to plan cost-effective future.

Iron is quite important for neurologic functioning and myelin sheath formation.^{2,3} Neurotransmitter metabolism and brain energy metabolism are affected negatively in iron deficiency, and iron replacement therapy is found to improve the mental development score.^{2,4,5} Previous studies showed that IDA in children contributed to the development of anxiety, depression, social and attention-deficit disorders.⁶ Similarly, an association between low serum ferritin levels and depres-

sion has been reported even in the absence of IDA.⁷

Functional dyspepsia (FD) is described as dyspeptic symptoms with no apparent physical and biochemical causes. It affects up to 40% of the general population and significantly reduces quality of life (QoL). Patients with FD seek medical attention.⁸ FD might be also caused by autonomic dysfunction, chronic distress, and anxiety.⁹ A close relationship between FD and depressive disorders has been suggested in recent psychiatric studies.^{10,11} Population-based surveys^{12,13} revealed that the most common problems in common practice were functional gastrointestinal disorders, and their population prevalence ranged from 12% to 25%. FD is thought to be a somatic condition, and its features cannot be fully explained by objective medical findings. Constipation is also a common bowel disturbance with a social perspective. It is a combination of heterogeneous, wide-spectrum symptoms; some of these symptoms might be classified into clinical entities, like the irritable bowel syndrome.^{14,15}

This study investigated the presence of FD, and symptoms of somatization and depression in IDA patients. In addition, the study evaluated the relation between FD and stress-related symptoms in IDA.

MATERIALS AND METHODS

A total of 125 consecutive IDA patients who were admitted to the Hematology and Internal Medicine outpatient clinics of Trakya University Medical Faculty, Edirne, Turkey, were included in the study. Only female subjects were included in the study because IDA is most prevalent in adult women, and female and male patients have different perceptions of depression. In the Turkish population, female patients make up the majority of hospital admissions for IDA; in fact, the number of males with IDA seen at the clinics is very low. Male IDA patients generally have many coexisting diseases that make their evaluation more cumbersome. All subjects included in the study were apparently healthy, and they had no prior history of any serious disease: none of them were being treated for any chronic disorder. Exclusion criteria were any other cause of anemia (hemoglobinopathies, anemia due to membrane defects, sideroblastic anemia, pernicious anemia), history of chronic disease (hematologic/solid malignancy, chronic renal failure, chronic liver disease, diabetes mellitus), history of abdominal surgery, psychiatric treatment within the last 6 months, and treatment for any other cause. All the participants were residing in Edirne, which is a city in northwestern Turkey, and all were of Turkish origin. In addition, 57 healthy female subjects were taken as a control group.

None of them had known IDA, and biochemical tests did not show any anemia in these patients. Local ethical committee approval was obtained.

Each patient was questioned about his/her demographic and clinical characteristics that included age, marital status, educational level, and concomitant diseases. To determine whole blood count, erythrocyte sedimentation rate, C-reactive protein, and standard parameters of iron status, a fasting venous blood sample was obtained from IDA patients. The CellDyn 3700 analyzer (Abbott GmbH&Co.KG, Abbott Diagnostics Europe, Wiesbaden, Germany) was used to obtain hemoglobin (Hb), mean corpuscular volume (MCV), red cell distribution width, hematocrit, and platelet values. Serum iron (SI) (normal range for males: 31-144 µg/dL, and for females: 25-156 µg/dL) and unsaturated iron-binding capacity (UIBC) (N: 110-370 µg/dL) were analyzed with spectrophotometric methods by the instrument, ARCHITECT c8000 System (Abbott Laboratories, Diagnostics Division, IL, USA). Total iron binding capacity (TIBC) was obtained by adding SI and UIBC. Transferrin saturation was calculated from the equation: (SI/TIBC) × 100%. Serum ferritin (SF) was determined using a chemiluminescence immunometric assay on the IMMULITE 1000 analyzer (Diagnostic Products Corporation, LA, USA). Normal ranges for ferritin concentration were 28 to 397 ng/mL for adult men and 6 to 159 ng/mL for women.

IDA was defined as Hb serum concentration of less than 12 g/dL in women (normal female adult 12.0–15.5 g/dL) with SF less than 12 ng/mL, low SI, raised TIBC, and TS <16%. High-performance liquid chromatography Hb electrophoresis was carried out in all the patients with MCV <76 fl. Subjects with HbA2 >3.5% were diagnosed with thalassemia minor.

The symptoms in the severity of dyspepsia assessment (SODA) questionnaire were used to define dyspepsia. SODA is a multidimensional dyspepsia measure.¹⁶ SODA was demonstrated to be an effective instrument for measuring dyspepsia-related health.¹⁷ All IDA patients and controls were asked to fill in SODA. Simply, SODA includes the severity of belching, reflux, gas, bloating, sour taste in the mouth, vomiting, and halitosis in the last month. Likert-type scale was used to define symptoms (0-4). In addition, patients marked on a visual analog scale the degree to which their QoL was disturbed because of dyspepsia (0: not affected at all; 100: affected negatively at the highest level possible). Self-reported constipation was investigated by asking each patient if he/she felt like being constipated for the last 12 months.

The screening for a somatization disorder was made by using the somatic symptom checklist (SSC) consisting of 7 items.¹⁸ The items in this scale are: trouble in breathing, frequent vomiting, loss of voice for more than 30 minutes, being unable to remember what you have been doing for hours or days (without any drug or alcohol intake), difficulty in swallowing, frequent pain in the fingers or toes, and frequent trouble with menstrual cramps. This checklist was originally validated as a screening test for somatization disorders.¹⁹ These symptoms were included in the American criteria for somatization disorders,¹⁸ and the total score was between 0 and 7.

The depression status of IDA patients was determined by using the Beck Depression Inventory (BDI), which was developed and revised by Beck et al.^{20,21} This 21-item self-reported questionnaire was originally used to assess the severity of depressive symptoms in the psychiatric population. Its reading level is of fifth or sixth-grade; therefore, it requires minimal time and no special training to administer. A previous study validated the Turkish version of BDI,²² and this validated form was used in the current study. The normal range is indicated by an index score of ≤9; minimal depressive symptomatology is indicated by scores from 10 to 15; mild depression is indicated by scores from 16 to 31; moderate depression is indicated by scores from 32 to 47; and severe depression is indicated by a score >47.²² The cut-off level to define depression was 16 points in this study.

Chi-square test was used to compare categorical variables. For the comparison of quantitative variables, unpaired t test was used. Correlation analysis was performed by Pearson test.

RESULTS

No differences were observed in mean age and marital status between IDA patients and controls. The mean bloating score was higher in IDA patients than in control subjects ($P<.001$). Other dyspepsia-related scores were similar in the IDA group and controls. The mean dyspepsia-related QoL disturbance score was higher in the IDA group than in control subjects ($P=.01$). The frequency of self-reported constipation was higher in the IDA group than in controls (56% vs 22.8%, $P<.001$). In IDA patients, the mean constipation-related QoL disturbance score was also higher than in controls ($P=.008$). The frequency of depression according to BDI and the mean SSC score in the IDA group was significantly higher than in controls ($P<.05$). The general clinical features of patients with IDA and control subjects are seen in **Table 1**.

According to BDI, 71 IDA patients had depression. When their whole blood count and ferritin and iron parameters were compared with others, no significant differences could be seen ($P<.05$). In addition, IDA patients with depressive symptoms had higher mean reflux ($P=.01$), bloating ($P=.009$), halitosis ($P=.001$), and dyspepsia-related QoL disturbance ($P=.001$) scores compared to others. These patients also had a higher self-reported constipation frequency and mean constipation-related QoL disturbance score (P values: .002 and $<.001$). IDA patients with depression had significantly higher SSC scores compared to others ($P=.001$). The general features of IDA patients with and without depression and the comparison of their GIS questionnaires are seen in **Table 2**.

In IDA patients BDI scores were correlated with mean reflux ($r=0.23$, $P=.009$), bloating ($r=0.26$, $P=.003$), gas ($r=0.21$, $P=.02$), sour taste ($r=0.19$, $P=.03$), nausea ($r=0.2$, $P=.028$), and halitosis ($r=0.25$, $P=.004$) scores. The BDI score had a moderate correlation with the SSC score ($r=0.45$, $P<.001$), and it correlated with dyspepsia ($r=0.29$, $P=.001$) and constipation-related QoL disturbance ($r=0.26$, $P=.003$) scores. BDI and SSC did not correlate with iron parameters in IDA patients.

Table 1. General clinical features of patients with iron deficiency anemia and controls.

	Iron deficiency anemia patients	Controls	P
n (%)	125	57	-
Age*	39.1 (13.6)	41.5 (8.6)	NS
Belching (0-4)*	0.6 (1.0)	0.5 (0.9)	NS
Reflux (0-4)*	0.7 (1.1)	0.7 (1.0)	NS
Bloating (0-4)*	1.0 (1.2)	0.4 (0.7)	<.001
Gas (0-4)*	0.6 (1.0)	0.6 (0.9)	NS
Sour taste (0-4)*	0.6 (1.0)	0.8 (1.0)	NS
Vomiting (0-4)*	0.6 (1.0)	0.4 (0.8)	NS
Halithosis (0-4)*	0.5 (0.9)	0.3 (0.8)	NS
Dyspepsia-related QoL disturbance (0-100)*	33.5 (36.3)	20.6 (27.7)	.01
Self-reported constipation, n (%)	70 (56)	13 (22.8)	<.001
Constipation-related QoL disturbance (0-100)*	28.4 (32.7)	15.6 (28)	.008
Depression (BDI>16), n (%)	71 (56.8)	6 (10.5)	<.001
Somatic symptom checklist score (0-7)*	2.1 (1.7)	1.1 (0.8)	<.001

NS: Not significant; QoL: quality of life; BDI: Beck Depression Inventory.

(*) denotes mean (SD) values.

Table 2. Iron parameters and GIS symptom severity in IDA patients with and without depression.

	IDA patients with depression	IDA patients without depression	P
n (%)	71 (56.8)	54 (43.2)	-
Hemoglobin (g/dL)*	10.7 (1.4)	10.0 (1.8)	.16
Iron (µg/dL)*	34.9 (20.7)	36.1 (37.8)	.91
Iron-binding capacity (µg/dL)*	439.8 (64.1)	422.2 (102.1)	.51
Ferritin (ng/mL)*	9.5 (14.3)	4.1 (2.1)	.27
Belching (0-4)*	0.7 (1.1)	0.4 (0.9)	.19
Reflux (0-4)*	0.9 (1.2)	0.4 (1.0)	.01
Bloating (0-4)*	1.2 (1.2)	0.7 (0.9)	.009
Gas (0-4)*	0.8 (1.1)	0.4 (0.8)	.04
Sour taste (0-4)*	0.7 (1.0)	0.5 (0.9)	.25
Vomiting (0-4)*	0.7 (1.1)	0.4 (0.7)	.12
Halitosis (0-4)*	0.7 (1.1)	0.2 (0.5)	.003
Dyspepsia-related QoL disturbance (0-100)*	42.8 (37.8)	21.8 (30.6)	.001
Self-reported constipation, n (%)	48 (67.6)	21 (39.6)	.002
Symptom-based constipation (≥2 criteria), n (%)	58 (81.7)	39 (56.6)	.002
Constipation-related QoL disturbance (0-100)*	35.9 (33.8)	17.2 (26.7)	<.001
Somatic symptom checklist score (0-7)*	2.7 (1.8)	1.4 (1.3)	.001

IDA: Iron deficiency anemia; QoL: quality of life; MCV: mean corpuscular volume; GIS: gastrointestinal system.

(*) Denotes mean (SD) values.

IDA patients had weak correlations between SSC and mean reflux ($r=0.23$, $P=.009$), bloating ($r=0.26$, $P=.003$), gas ($r=0.21$, $P=.02$), sour taste ($r=0.19$, $P=.03$), nausea ($r=0.2$, $P=.028$), and halitosis ($r=0.25$, $P=.004$) scores. The BDI score had a moderate correlation with the SSC score ($r=0.45$, $P<.001$), while it had a correlation with the constipation-related QoL disturbance ($r=0.26$, $P=.003$).

DISCUSSION

Bloating and FD-related QoL disturbance scores were higher in IDA patients in this study. In addition, IDA patients had a significantly higher frequency of self-reported constipation and a higher mean score of constipation-related QoL disturbance. The study revealed significant associations between the presence of constipation and FD-related symptoms, and also the presence of depression and somatization in IDA. Symptoms that

were more significantly associated with the presence of depression were reflux, bloating, gas, and halitosis. In addition, significant relationships were observed between depression and somatization scores and between FD and constipation-related QoL disturbance.

Physical functioning, which is one of the domains of QoL, was reported to be worse in IDA patients in a couple of studies.²³⁻²⁵ One of these studies concluded that depressive symptoms in eating disorders, including anorexia, could be explained with iron deficiency.²⁶ In another study, the correction of anemia in females with heavy menstrual bleeding resulted in the improvement in QoL.²⁵ One previous study reported that low SF levels, in the absence of anemia, could be associated with the presence of depression.¹ This study found no association between ferritin and any iron parameters or somatization score.

There are studies that have reported cognitive dysfunction in IDA patients; the presence of sleep disturbances and attention deficit, and hyperactivity disorders and their improvement with iron replacement therapy in children are also known.²⁷ In addition, IDA was suggested to be associated with nonspecific symptoms like fatigue and irritability; however, this has not been proven. It was also reported that there was an increased prevalence of chronic widespread pain associated with stress and somatization in IDA patients.²⁸

Furthermore, IDA patients are generally prone to explain their nonspecific complaints with anemia. Nevertheless, the results of this study show that GIS symptoms in IDA are more strongly related to the presence of depression and somatization rather than the degree of anemia and iron parameters.

Based on the results of this study, one should take caution before embarking on extensive investigations of gastrointestinal symptoms, as they may be more reflective of somatization and depression that occur with increased frequency in IDA patients. One should look for more objective data like chronicity of symptoms, weight loss, and family history of cancer and take a deeper look at the psychiatric history of the patient especially those in the otherwise healthy young age group of the female gender.

The limitations of this study are as follows: (1) the absence of long-term follow-up for GIS-related symptoms. However, this study provides important cross-sectional data about IDA; (2) the inclusion of a relatively small healthy control size. It was mentioned that there should be at least a difference of 8 to 10 units on a 100-unit scale for small sample sizes to achieve statistically significant results in the interpretation of questionnaire. Thus, significant differences between

groups could be skipped because of small sample size; (3) the inclusion of IDA patients who were referred to a tertiary center; this might have led to a higher frequency of depression and somatization symptoms; (4) the inclusion of randomly selected IDA patients in the population could have revealed more accurate results. However, the design of such a trial is quite difficult; (5) non-evaluation of depression and somatization in control subjects. However, the primary aim of this study was to evaluate the relationship between GIS symptoms and psychiatric situation in IDA patients; and (6) the depression and somatization score of the IDA patients after iron therapy was not evaluated.

In conclusion, patients with IDA have a higher oc-

currence of gastrointestinal symptoms namely bloating and constipation. This increased occurrence could be related to an underlying increased incidence of somatization and depression. Therefore, the evaluation of FD and its associated symptoms is an important component in the approach to IDA patients. One should take caution before embarking on extensive investigation of gastrointestinal symptoms in such patients. Moreover, a detailed psychiatric history is highly recommended.

Conflict of interest

The authors declare no potential conflicts of interest for this article.

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