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Micronutrient deficiency among patients with ulcerative colitis

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Abstract

Background and aim: Malnutrition is a common problem among patients with inflammatory bowel disease and up to 18–62% of ulcerative colitis (UC) patients were reported to be malnourished. This study aimed to assess micronutrient status among naïve UC patients and its correlation with disease severity.

Methods: A prospective case-control study carried out on 46 patients who visited our endoscopy unit between April 2019 and April 2021. The patients were classified into 3 groups of mild, moderate, and severe UC based on colonoscopy findings, and histopathological examination. Serum was collected and assayed for levels of iron, magnesium, zinc, selenium, and copper.

Results: Forty-six (17 male, 29 female) patients divided into 2 groups (23 naïve UC patients and 23 healthy individuals) with the mean age of 32 years were included in the study. The serum levels of magnesium, zinc, and selenium were significantly lower in the UC group ($p < 0.001$, 0.018 and < 0.001, respectively). However, iron and copper levels were not significantly different between the 2 groups. In discriminating severe from mild-moderate UC cases, there was a statistically significant result of magnesium at cutoff 1.8 or less in discriminating severe from mild to moderate UC cases with an AUC of 0.950 and p value of < 0.001.

Conclusion: Micronutrients should be assessed in patients in UC patients to alert to the fact that correction of these deficiencies could facilitate achievement of remission. Further research is needed to confirm if magnesium levels could serve as a predictor of the disease severity.

Keywords: Ulcerative colitis, Micronutrients, Malnutrition

Background

Ulcerative colitis (UC) is chronic gastrointestinal inflammation with alternating relapsing and remitting episodes [1]. UC often present with a combination of diarrhea, abdominal pain, rectal bleeding, weight loss, and malaise [2]. Diagnosis of ulcerative colitis is made clinically with supportive findings on colonoscopy, histopathological examination, and by negative stool examination for infectious causes [3].

Malnutrition is a common problem among patients with inflammatory bowel disease and up to 18–62% of UC patients were reported to be malnourished [4]. Regarding the chronic nature of the disease, there is a likelihood of micronutrient deficiency due to chronic diarrhea, reduced food intake (in the case of dietary restrictions, anorexia, nausea, and vomiting), poor nutritional support, increased intestinal excretion, bloody bowel movement, and drug interactions [5]. Thus, this study aimed to assess micronutrient status among naïve UC patients and its correlation with disease severity.

Methods

This is a prospective case-control study carried out on 46 patients divided into 2 groups (23 naïve UC patients and 23 healthy individuals) who visited our endoscopy unit

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between April 2019 and April 2021. The inclusion criteria for the UC group were newly diagnosed patients by colonoscopy and confirmed by histopathology. The exclusion criteria were patients with UC under treatment, non-specific colitis and patients with chronic illness or neoplasm of any system. Healthy individuals were those who underwent colonoscopy for any other causes such as chronic abdominal pain, chronic constipation and anemia whose endoscopy showed normal mucosal pattern with normal histopathological examination. The study protocol was approved by our ethical committee, and written consents were obtained from all patients before the procedure.

All the UC patients underwent an accurate physical examination and history taking. The patients were classified into three groups of mild, moderate, and severe UC based on clinical evaluation by an expert gastroenterologist, as well as laboratory, colonoscopy findings using Mayo score [6] and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [7], and histopathological examination.

The laboratory investigations were done at our clinical immunology laboratories. Blood samples (5 ml) were drawn from UC patients and control group on plain tube and left to clot for 20 min. The samples were centrifuged at 2500 rpm for 10 min and serum was collected and stored at 20 c until assay for serum level of iron, magnesium, zinc, selenium, and copper. Copper was measured by colorimetric method with Diborm-PAESA. Zinc was measured using colorimetric method with 5-BROMO-PAPS. Iron was measured by colorimetric CAB method. Magnesium was measured by phosphanzo III, colorimetric endpoint. Selenium was measured using ELIZA technique.

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The sample size was determined to be 26 in the 2 groups of healthy individuals ($n = 13$) and UC patients ($n = 13$), according to the results of Ojuawo et al. [8] and based on the difference between 2 population means. Qualitative data were expressed as N (%). Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p > 0.050$. Presence of significant outliers (extreme values) was tested for by inspecting boxplots. Quantitative data were expressed as mean, standard deviation (SD), and standard error (SE) or median, range (maximum−minimum), and interquartile range (IQR = 75th percentile−25th percentile).

Chi-square test was used to test the association between two nominal variables. Chi-square test was used when the expected count in all cells was ≥ 5, otherwise, Fisher's exact test was used. Independent-samples t test was used to compare normally distributed quantitative data between two groups. The Pearson correlation test was used to determine whether there is a linear relationship/association between two normally distributed quantitative data. The strength of association was considered low, medium, or high if the correlation coefficient (r) was > 0.1 to < 0.3, 0.3 to < 0.5, or 0.5 or more, respectively. The Spearman's correlation test was used to determine whether there is a linear relationship/association between two non-normally distributed quantitative data. The strength of association was considered low, medium, or high if the correlation coefficient (r_s) was > 0.1 to < 0.3, 0.3 to < 0.5, or 0.5 or more, respectively. For any of the used tests, results were considered as statistically significant if p value ≤ 0.050. Appropriate charts were used to graphically present the results whenever needed.

Results

Forty-six (17 male, 29 female) patients with the mean age of 32 years were included in the study. The 2 groups (23 naïve UC patients and 23 healthy individuals) were homogeneous in terms of age, gender and place of residence. The serum levels of magnesium, zinc, and selenium were significantly lower in the UC group. However, iron and copper levels were not significantly different between the two groups. There was a statistically significant higher WBCs count in UC group compared to control group (Table 1). Clinical characteristics and histopathological findings in UC patients are shown in Table 2. Grading of disease severity by histopathological examination showed that only two cases (8.7%) were mild

Table 1 Comparisons of categorical and quantitative variables between the two study groups

Characteristic	UC group	Control group	*P* value
Male	10 (43.5%)	7 (30.4%)	0.359
Female	13 (56.5%)	16 (69.6%)	
Rural	8 (34.8%)	11 (47.8%)	0.369
Urban	15 (65.2%)	12 (52.2%)	
Age (years)	33 (25–40)	31 (27–35)	0.930
Hemoglobin (g/dl)	11.1 ± 1.8	11.4 ± 1.7	0.473
WBCs count (× 10^3 per mm^3)	8.4 ± 2.7	6.9 ± 2.4	**0.048**
Platelet count (× 10^3 per mm^3)	260 (210–297)	250 (183–279)	0.758
Serum selenium (pg/ml)	145.7 ± 58.8	536.2 ± 182	**< 0.001**
Serum Zinc (µg/dl)	62.1 ± 17	76.9 ± 23.3	**0.018**
Serum copper (µg/dl)	87.9 ± 11.4	85 ± 12.7	0.412
Serum iron (µg/dl)	97.2 ± 37.9	101.5 ± 27.1	0.660
Serum magnesium (mg/dl)	1.9 (1.8–2.0)	2 (2–2.1)	**< 0.001**

Table 2 Clinical characteristics and histopathological findings of UC patients

Numeric characteristic	Median (Q1–Q3)
Stool frequency (motion per day)	4 (3–7)
Duration of illness (months)	1 (1–2)
Categorical characteristic	*N* (%)
Presence of blood in stool	16 (69.6%)
Occurrence of weight loss	8 (34.8%)
Presence of abdominal pain	18 (78.3%)
Histopathological findings	*N* (%)
Atypia	1 (4.3%)
Granuloma	0 (0%)
Malignancy	0 (0%)
Cellular infiltrate	23 (100%)
Cryptitis	23 (100%)
Crypt abscess	18 (78.3%)
Irregular shape of crypts	23 (100%)
Severity on biopsy	
Mild	2 (8.7%)
Moderate	11 (47.8%)
Severe	10 (43.5%)

while the disease was moderate, and severe in 47.8% and 43.5%, respectively.

There was a statistically significant negative correlation between serum magnesium and severity indices (Mayo score, UCEIS, ESR, and CRP) in UC patients. The strength of association was moderate for CRP, and large for others. There was no significant correlation of any studied micronutrient with neither disease duration nor disease extent (Table 3). Correlations of micronutrients with laboratory parameters in UC patients showed a statistically significant negative correlation of medium strength between iron and age, and a statistically significant positive correlation of medium strength between zinc and hemoglobin (Table 4).

In discriminating severe from mild-moderate UC cases, there was a statistically significant result of magnesium at cutoff 1.8 or less in discriminating severe from mild to moderate UC cases with an AUC of 0.950 and p value of < 0.001 with sensitivity 100% and specificity 83.3% (Fig. 1).

Table 3 Correlations of micronutrients with severity indices in UC patients ($N = 23$)

Parameter	Serum selenium		Serum zinc		Serum copper		Serum iron		Serum magnesium	
	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value
Mayo score (ordinal)	0.175	0.426	0.061	0.784	− 0.142	0.518	0.198	0.366	− 0.814	**< 0.001**
Mayo score (numeric)	0.079	0.719	− 0.006	0.977	− 0.036	0.870	0.178	0.416	− 0.714	**< 0.001**
UCEIS	0.103	0.641	− 0.364	0.087	− 0.056	0.800	0.120	0.585	− 0.651	**< 0.001**
Disease duration (months)	0.026	0.906	0.031	0.887	− 0.169	0.439	0.335	0.118	0.307	0.154
ESR	0.023	0.915	0.019	0.930	0.173	0.431	0.238	0.274	− 0.701	**< 0.001**
CRP	0.033	0.880	285	0.187	− 0.042	0.850	0.048	0.828	− 0.425	**0.043**

r_s Spearman's correlation coefficient. Test of significance is Spearman's correlation test

Table 4 Correlations of micronutrients with laboratory parameters in UC cases ($N = 23$)

Parameter	Selenium		Serum zinc		Serum copper		Serum iron		Serum magnesium	
	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value
Serum selenium	–	–	0.248	0.096	0.035	0.818	0.075	0.621	− 0.188	0.391
Serum zinc	0.248	0.096	–	–	− 0.069	0.650	0.145	0.338	0.126	0.567
Serum copper	0.035	0.818	− 0.069	0.650	–	–	0.033	0.829	0.119	0.588
Serum iron	0.075	0.621	0.145	0.338	0.033	0.829	–	–	− 0.117	0.596
Serum magnesium	0.521	0.391	0.090	0.553	0.027	0.860	0.132	0.382	–	–
Age	0.041	0.787	− 0.090	0.551	0.092	0.544	− 0.458	**0.001**	0.046	0.836
Hemoglobin	0.066	0.664	0.347	**0.018**	− 0.145	0.335	0.265	0.075	0.006	0.977
WBCs count	− 0.274	0.065	− 0.171	0255	− 0.070	0.644	− 0.269	0.071	− 0.150	0.496
Platelet count	− 0.120	0.425	− 0.267	0.072	0.121	0.422	− 0.107	0.477	− 0.240	0.270

r_s Spearman's correlation coefficient. Test of significance is Spearman's correlation test

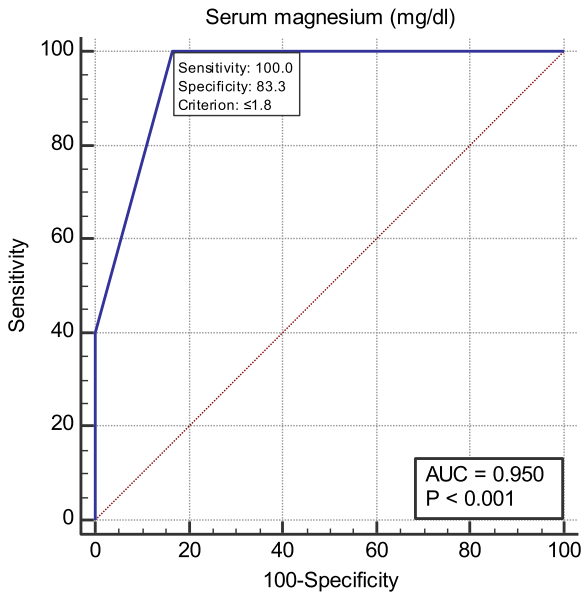

Fig. 1 ROC curve for cut-points of magnesium in discriminating severe from mild-moderate disease activity

Discussion

Malnutrition can be classified as macronutrient or micronutrient deficiency. Macronutrient deficiency is determined by protein–energy malnutrition and usually affects patients with active and severe disease [9]. Micronutrient deficiency may impact the immune system and predispose to the onset and progression of UC [10]. The inflammatory signaling pathways are influenced by many micronutrients including selenium, zinc, copper, and iron [11]. Selenium is a component of many essential enzymes and regulates growth processes. It also shows antioxidant activity and guards cells against the harmful effects of free radicals [12]. Zinc modulates the immune function, facilitates protein and DNA synthesis, supports the catalytic activity of numerous enzymes, and improves intestinal barrier function [13]. Copper is an essential cofactor for enzymes and electron transport proteins required for neurotransmitters, antioxidants, and oxidative phosphorylation, as well as iron transport [14]. Iron deficiency, the most common systemic complication in UC, leads to impaired cytokine production by lymphocytes and defective T cell proliferative response [15]. Unfortunately, there is little evidence on the clinical importance of micronutrients and their routine assessment in UC patients.

Our findings showed that UC patients had significantly lower serum magnesium levels, as well as zinc and selenium levels, when compared to healthy subjects. There was no significant difference in serum copper and iron levels between the two groups. Similar to our results, Siva et al. [16] and Mohammadi et al. [17], found that the zinc deficiency was frequently observed in patients with UC. Zinc deficiency is not only explained by mucosal damage and malabsorption but also owing to poor nutritional support as a symptom of active disease. However, Joshaghani et al. [18] showed serum zinc levels did not differ significantly between the UC patients and the healthy subjects.

As regard selenium, Castro Aguilar-Tablada et al. [19] conducted a study on 53 UC patients that showed significant lower serum selenium level compared to healthy controls; consistent with our results. This could be explained by poor nutritional support, reduced food intake due to anorexia, nausea, vomiting, abdominal pain, dietary restrictions, and chronic diarrhea. However, Joshaghani et al. [18] conducted a cross-sectional study on 60 recently diagnosed UC patients that showed no significant difference in selenium levels between the UC patients and the control subjects.

As regards magnesium, Geerling et al. [20] showed that the mean serum level of magnesium was significantly lower in the patients with active UC compared to the controls; consistent with our results. Magnesium deficiency occurs mostly due to reduced food intake, active inflammation, malabsorption, and enteric loss of nutrients that may together lead to abnormal antioxidant status. Our results showed a statistically significant result of magnesium at cutoff 1.8 or less in discriminating severe from mild to moderate UC cases with an AUC of 0.950 and p value of < 0.001 with sensitivity 100% and specificity 83.3%, while the serum levels of zinc, iron, and selenium, and copper were not associated with disease severity. Similarly, Joshaghani et al. [18] showed that low serum magnesium level was seen in 80% of the patients with active UC, 66.7% of the patients with inactive UC and 40% of the healthy controls (P < 0.005). However, Kalantari et al. [21] showed no significant correlation of magnesium with the disease activity. Also, there was no significant correlation of serum copper, zinc, and iron with the disease severity.

As regards copper, Poursadegh et al. [5] and Shokrzadeh et al. [22] found no significant difference in copper levels between the UC patients and the control subjects; consistent with our results. This could be attributed to due to an elevation in ceruloplasmin level in response to inflammation. On the contrary, Joshaghani et al. [18] found that the mean serum level of copper was significantly lower in the patients with active UC compared to the control subjects.

As regard disease duration, there was no significant correlation of any of studied micronutrient with disease duration, this may be attributed to recent onset of the disease in all cases. Similar to our study, Kalantari et al.

[21] showed no significant correlation of disease duration with the studied micronutrients.

Our study showed a statistically significant strong positive correlation between serum zinc and hemoglobin as zinc affect hemoglobin via several zinc-dependent enzyme systems involved in erythropoiesis stimulation and hemoglobin synthesis. In a cross-sectional study conducted on 12 countries, zinc concentrations were independently and positively associated with hemoglobin concentrations in roughly half of the countries examined suggesting that strategies to contest zinc deficiency may help to reduce the prevalence of anemia [23].

Also, our study showed a statistically significant strong negative correlation between serum iron and patient age. Similarly, another descriptive analytical cross-sectional study conducted on UC patients showed negative correlation between serum iron and patient age [21]. Chronic inflammation in older people, poor dietary intake, and elevated levels of circulating hepcidin are responsible for changes in iron metabolism that result in systemic iron depletion [24].

The present study has some limitations. First, the number of patients included in the study was relatively small; with small number of patients with mild UC that make it difficult to detect differences in micronutrient status between patients with mild and moderate to severe UC. Second, it was a single tertiary center experience that does not allow to generalize the conclusion. On the other hand, we studied naïve UC patients before any dietary restrictions, or any nutritional supplements incorporated in the patient's medications.

Conclusion

Micronutrients should be assessed in patients in UC patients not only to guide the decision on supplementation but also alert to the fact that correction of these deficiencies, which impair the immune response, could facilitate achievement of remission. Further research is needed to confirm if magnesium levels could serve as a predictor of the disease severity or in discrimination of severe from mild to moderate UC.

Abbreviations

UC: Ulcerative colitis; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; SD: Standard deviation; SE: Standard error; IQR: Interquartile range; WBCs: White blood cells; CRP: C reactive protein; AUC: Area under the curve.

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None

Authors' contributions

AH made substantial contributions to the design of the work, analysis and interpretation of the data. SA made substantial contributions to the design of the work, supervising the work and in doing the statistical analysis of the data. SA and AA had major contribution in revising the work. AA is the corresponding author, has a major role in collecting the data, the endoscopic procedure of the patients in the study, and had a major role in writing the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Board of our University, and informed written consent was obtained from all participants according to the Declaration of Helsinki.
The committee's reference number is MS.19.03.516 (approval date: 16/3/2019).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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