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Article

Salivary trace elements in patients with ulcerative colitis on different treatment modalities

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ABSTRACT

The nutritional status of patients with inflammatory bowel disease is considered less than ideal. This study aimed to compare the salivary levels of some trace elements (Zinc, copper, and magnesium) in patients with ulcerative colitis (UC) on two different therapeutic modalities to control subjects. Materials and methods: This cross-sectional study was performed in 2021-2022 on 53 diagnosed UC patients (27 UC patients on oral immunosuppressant therapy and 26 UC patients on combination therapy). All subjects were randomly selected from gastroenterology and Hepatology teaching hospitals in Baghdad city; twenty-five subjects were also recruited as controls. Demographic data were recorded through a checklist. Salivary levels of zinc (Zn), copper (Cu) and magnesium (Mg) were measured by atomic absorption spectroscopy. Data were analyzed using SPSS-28 at a significance level of 0.05. The results: Salivary Zn mean was significantly lower in monotherapy and combination therapy patients than in controls ($p<0.001$). Mean salivary Cu levels were significantly higher in monotherapy and combination therapy patients than in controls ($p<0.001$). Similarly, the salivary Mg mean was significantly lower in both groups of ulcerative colitis patients than in controls ($p<0.001$). The mean of salivary Cu was higher in UC patients, while the men of Zn and Mg were lower in UC patients compared to controls. Conclusions: The results showed that UC patients have significantly lower Zn and Mg levels than healthy individuals and were lower inpatient on monotherapy than in combination. At the same time, salivary Cu in UC patients was higher than in control individuals and was higher in UC patients on monotherapy.

Keywords: Inflammatory bowel diseases, Ulcerative colitis, Trace elements

INTRODUCTION

Inflammatory bowel diseases (IBD) are caused by improper mucosal immune system function, including ulcerative colitis (UC) and Crohn's disease [1]. The global UC incidence ranges from 2.2 to 3.14 per 100,000 people per year, while the global Crohn's disease incidence ranges from 1.3 to 6.14 per 100,000 people per year [2]. The exact cause of the disease is unknown, but several factors,

including bacteria, nutrition, psychology, immunology, genetics, and environmental factors, have been implicated in IBD pathogenesis. Immunological processes, cytokines, and the complement system have all been linked to an increased risk of IBD [3]. Nutrient deficiency in IBD patients is known to be caused by weight loss, malabsorption, diarrhea, systemic inflammation, hypermetabolic state, and adverse drug reactions. In these patients, nutritional status is less than optimal, and signs and symptoms of this problem may appear months or years later [4]. Inadequate trace element and mineral levels can also compromise the host's defense mechanisms against oxidative damage caused by free radicals. Mineral metabolism is altered in IBD patients, primarily during flare-ups. Trace elements, particularly copper (Cu) and zinc (Zn), may impair the mucosa's ability to deal with the harmful effects of free radicals [5]. In enterocytes and hepatocytes, Zn is required for biological functions such as homeostasis, metabolism, absorption, and intracellular transport. Zinc ions are required for the structural stability of some metalloproteins. Zinc is also thought to be important in maintaining intestinal integrity. Through nitric oxide inhibition, zinc plays an anti-inflammatory role in intestinal inflammation [6]. Copper is required for iron absorption, storage, and metabolism. Copper deficiency and anemia have similar symptoms. Cu absorption occurs in the stomach and intestinal walls. It is a powerful antioxidant that eliminates free radicals and prevents cell damage [7]. Magnesium (Mg) is a trace element required for synthesizing RNA, DNA, and protein. Mg's most important functions include the regulation of muscle contraction, blood pressure, insulin metabolism, cardiac irritability, nerve conduction, and neuromuscular transmission [8]. Considering the importance of these elements, this study was designed to evaluate their levels in patients with UC and healthy control individuals without intestinal pathology.

MATERIALS AND METHODS

This study compared the salivary level of some trace elements (Zinc, copper, and magnesium) in patients with ulcerative colitis (UC) on two therapeutic modalities and compared to 25 control subjects.

Ethical Approval

This research was approved by a Research Ethics Committee/ University of Baghdad/ College of Dentistry according to a decision report (Ref. Number: 440/ Date 3-1-2022).

THE SAMPLE

Seventy-eight participants were enrolled in this study, of which fifty-three were endoscopically and histologically diagnosed with ulcerative colitis at least 3 months before starting this study. In contrast, twenty-five subjects were healthy and were age and gender-matched control group. The inclusion criteria for which ulcerative colitis patients were enrolled in this study were based on therapeutic options that were decided according to the severity of the disease. This study selected 53 patients with moderate to severe ulcerative colitis and divided into 2 groups according to the treatment. The study groups are:-

1-Group 1: Twenty-six ulcerative colitis patients on oral immunosuppressant therapy (Azathioprine 50mg twice daily).

2-Group 2: Twenty-seven ulcerative colitis patients on the combination therapy of intravenous infusion of anti-TNF-α (Infliximab 5mg/kg every 8 weeks) plus oral immunosuppressant (Azathioprine 50mg twice daily).

3-Group 3: Twenty-five healthy-looking subjects without signs and symptoms of systemic diseases.

The exclusion criteria for all participants included any underlying systemic diseases (diabetes mellitus and hypertension), pregnant women and a history of radio or chemotherapy. All subjects were selected from the gastroenterology and Hepatology teaching hospital in Baghdad City from December 29th, 2021, to April 7th, 2022. The laboratory work on trace elements was done in the Poisoning consultation center Gazi Hariry Hospital.

Unstimulated whole saliva was collected from each subject after oral examination; saliva was centrifuged, and the supernatant layer was aspirated.

Determination of Trace elements

Frozen saliva was allowed to thaw at room temperature. Assessment of inorganic elements (Zn, Cu, Mg) was performed by Flam atomic absorption spectrometry (FAAS), the difference only in (Zn, Cu), saliva was diluted with distilled water, while in (Mg) saliva was diluted with lithium chloride.

Statistical analysis

Data analysis was carried out using the available statistical package of SPSS-28 (Statistical Packages for Social Sciences- version 28 at a significant level $p<0.05$). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

RESULTS

The mean age ±S. The D of UC patients on monotherapy was 35. 3±9. 2 years, the range of age was (20-49) years, on combination therapy was 30. 7±8. One year, the range of age was (20-49) years and in healthy control subjects, the mean age ±S. D was 27. 2±7. 9 years, the range of age was (20-46) years.

The number of female patients was 26 (48.8), while the male was 27 (51.2%); no significant difference was found.

There was no significant difference in the mean age and male-to-female percentage between the two groups of UC patients and the controls (Table 1) and (Table 2), respectively.

		Monotherapy "Azathio-prine"		**Combination "Azathio-prin& (In-fleximab) "**		**Healthy control**		**P value**
		No	%	No	%	No	%	
Age (years)	20---29	8	29.6	13	50.0	16	64.0	0.102
	30---39	10	37.0	8	30.8	7	28.0	NS
	40---49	9	33.3	5	19.2	2	8.0	
	Mean±SD (Range)	35.3±9.2 (20-49)		30.7±8.1 (20-49)		27.2±7.9 (20-46)		
Mean age ±SD of UC patients 33±8. 9, range (20-49)								

Table 1. The mean age and standard deviation of the three study groups. NS: non-significant P>0.05

		Monotherapy "Azathio-prine"		***Combination Azathioprin& (Infleximab)***		***Total***		***Healthy control***		***P value***
		No	*%*	*No*	*%*	*No*	*%*	*No*	*%*	
Gender	*Male*	*10*	*37.0*	*17*	*65.4*	*27*	*51.2*	*16*	*64.0*	*0.065*
	Female	**17**	**63.0**	**9**	**34.6**	**26**	**48.8**	**9**	**36.0**	**NS**

Table 2. Gender distribution of the study groups. NS: non-significant P>0.05

Salivary zinc (Zn):-

This study showed that the mean±SD and range of salivary zinc of ulcerative colitis patients on monotherapy treatment were 1.84 µg/del (±0.36) (1.20-2.60) µg/dL, respectively, and ulcerative colitis patients on Combination therapy 2.47 µg/dL (±0.55), (1.70-3.60), while of the control subjects were 3.308 µg/del (±0.59) (2.40-4.50).

Statistical analysis showed that salivary Zn was significantly higher in control subjects than in ulcerative colitis patients ($p< 0.001$) (Table 3).

This study showed that the mean level of salivary zinc was significantly lower in UC patients on monotherapy than patients on combination (Table 4) using a t-test.

Salivary copper (Cu):-

The results showed that the mean, ±SD and range of salivary copper in ulcerative colitis patients on monotherapy treatment were 6.02 µg/del (±0.77) (4.60-7.30), respectively. Also, It has been shown that the mean and standard deviation and range of copper in patients on combination treatment were 5.10 µg/del (±0.70) (3.60-6.8), while in the control subjects, mean and standard deviation were 3.97 µg/dL (±0.61), the range was (2.70-5.30) Table (3).

Statistical analysis showed that salivary copper was highly significantly increased in two groups of ulcerative colitis patients of this study than in the control subjects ($p<0.001$) using the ANOVA test (Table 3).

By using a t-test, the results showed that the mean of the saliva Cu level was highly significantly higher in UC patients on monotherapy ($p<0.001$), (Table 4).

Salivary Magnesium (Mg):-

This study showed that the mean±SD and range of salivary magnesium of ulcerative colitis patients on monotherapy treatment were 0.52 mg/dL (±0.07) and (0.41-0.67) mg/dL respectively, in ulcerative colitis patients on Combination therapy was0. 580 mg/dL (±0.09) and rang (0.36-0.74), while in the control subjects was 0.73 mg/dL (±0.12) and the range was (0.53-0.97) mg/dL.

Statistical analysis showed that salivary magnesium was highly significantly decreased in ulcerative colitis patients on two group treatment modalities than that in control subjects ($p< 0.001$) (Table 3)

This study found that the mean level of salivary Mg was significantly lower in UC patients on monotherapy than patients on combination (Table 4).

	Mean±SD	(Range)	Mean±SD	(Range)	Mean±SD	(Range)	
Saliva Zn (µg/dL)	1.84±0.36	(1.20-2.60)	2.47±0.55	(1.70-3.60)	3.30±0.59	(2.40-4.50)	0.0001^
Saliva Cu (µg/dL)	6.02±0.77	(4.60-7.30)	5.10±0.70	(3.60-6.80)	3.97±0.61	(2.70-5.30)	0.0001^
Saliva Mg (mg/dL)	0.52±0.07	(0.41-0.67)	0.58±0.09	(0.36-0.74)	0.73±0.12	(0.53-0.97)	0.0001^

Table 3. Mean ±SD and range of salivary Zn, Cu and Mg in two groups of ulcerative colitis patients and control subjects.*Significant difference among more than two independent means using ANOVA-test at 0.05 level.*

All variables (Age, Zn, Cu, and Mg) in this study were analyzed using t-test and ANOVA to compare the control and ulcerative colitis patient groups categorized according to treatment into Azathioprine monotherapy and combination groups.

Statistical analysis results using an ANOVA test showed highly significant differences ($p<0.001$) regarding Saliva (Zn, Cu, and Mg) (Table 4).

Containing analysis using a t-test, the results showed a significant difference in age between patients on monotherapy and healthy control and saliva Mg between patients on monotherapy and combination therapy ($p<0.05$).

Saliva Zn, Cu, and Mg also showed a highly significant difference between patients in the monotherapy and control group, patients on combination therapy, and patients on combination therapy and healthy control subjects (table 4).

Regarding treatment modalities, the results showed that salivary Zn and Mg were significantly lower in UC patients on monotherapy than in patients on combination. At the same time, saliva Cu was significantly higher in UC patients on monotherapy.

T-test & ANOVA	All Groups	Mono x Healthy	Comb x Healthy	Mono x Comb
Age (years)	0.004^	0.002#	0.129	0.061
Zn (µg/dL)	0.0001^	0.0001#	0.0001#	0.0001#
Cu (µg/dL)	0.0001^	0.0001#	0.0001#	0.0001#
Mg (mg/dL)	0.0001^	0.0001#	0.0001#	0.026#

The#Significant difference between two independent means using Students-t-test at 0.05 level.

Significant difference among more than two independent means using ANOVA-test at 0.05 level.

Table 4. Statistical analysis using t-test & ANOVA of the study parameters in ulcerative colitis patients and control subjects.P<0.001: high significance.

DISCUSSION

The results of this study showed that the mean age of UC patients was 33.0 years, with an age range (20-49) years. These results disagree with other Iraqi studies [24] who study salivary assessment of interleukin-6, C-reactive protein and albumin in ulcerative colitis patients concerning oral findings, saliva samples were taken from subjects of age range from (40-50) years, and disagree with other Iraqi studies [27] who study serum carcinoembryonic antigen and il-6 levels in serum patients with ulcerative colitis, in those studies included 35 patients with UC, mean age of (41.4± 15.7) years, ranged between (18-). This result also disagrees

with other Iraqi studies [of 26] who study Ulcerative Colitis Patients. The studied patients ranged between 18–58 years, with a mean age group of 36 (± 9.9).

The results of this study showed that the gender distribution of ulcerative colitis patients was 27 (51.2%) male and 26 (48.8%) female. This result agrees with other Iraqi studies [25] his study, Prevalence of ulcerative colitis patients, in which the male-to-female ratio of this study was 1: 1.

Only a few studies exist in which saliva trace elements of UC patients have been investigated; most of the studies dealt with serum trace elements of UC patients.

This study showed a statistically significant difference between controls and UC patients in salivary Zn, Cu, and Mg levels. The mean salivary Zn level differed significantly between the two groups of UC patients, with the control group having a higher level. Patients had lower Zn levels than controls. Crohn (1932) conducted the first study of Zn levels in IBD patients and discovered that Zn levels were significantly lower than healthy individuals [12]. This finding has been repeated in subsequent studies [13 14].

This study showed that salivary zinc was highly significantly decreased in ulcerative colitis patients on monotherapy treatment at 1.84 µg/del (±0.36) (1.20-2.60) µg/dL and in ulcerative colitis patients on Combination therapy was2. 47 µg/del (±0.55) (1.70-3.60) (2.03±0.58 mcg/del) than that of control subjects 3.30 µg/del (±0.59) (2.40-4.50).

Also, this study showed that the mean level of salivary Zn and salivary Mg was significantly lower in UC patients on monotherapy than patients on combination. In comparison, the mean level of salivary copper was significantly higher in UC patients on monotherapy. The value of results in the combination group is nearly the value of healthy control subjects, and this may be because the effect of combination therapy was better than the effect of monotherapy. To our knowledge, no previous studies were found regarding this subject.

This finding agreed with the findings of the study done by [12]. Who found that the serum zinc level in UC patients was significantly lower than in controls. These effects may be due to trace element abnormalities, which are most likely the result of inadequate intake, reduced absorption, and increased intestinal loss due to impaired absorption due to the inflammatory process. Zinc deficiency may contribute to the ongoing inflammatory process of IBD by reducing its free radical scavenging action and [12].

This study supported the findings of [13], who discovered that serum zinc concentrations were significantly lower in UC patients compared to controls, and it demonstrated that the nutritional status of IBD patients was already negatively impacted at the time of diagnosis.

This study contradicts the findings of [15] and [16] studies that found men and women with ulcerative colitis had significantly higher serum zinc concentrations than controls and also disagreed with the findings of the [18] study, which found that serum Zn levels do not differ significantly between UC patients and controls, this could be due to subjects being of better nutritional status and supplementation, or it could be due to the small sample size.

The result of this study showed that salivary copper was more significantly increased in two groups of ulcerative colitis patients than in the control subjects ($p<0.001$), which agrees with the study of [16] who found that the mean concentrations of serum copper were significantly higher ($P = 0.0001$) either in active or in inactive disease compared with healthy controls, this study explains that even in well-nourished patients with UC, high serum levels of copper was present, the latter alterations of copper are correlated with hematological parameters of relapse of the disease or with acute phase proteins suggesting a

relationship with the inflammatory process of UC. It has been shown that serum concentrations of Cu can be sufficiently high in IBD patients with a good nutritional status [16]. Also, agree with [15] studies that noticed an increased serum level of copper in ulcerative colitis patients.

[18] found that serum concentrations of Cu can be sufficient to be high in IBD patients with a good nutritional status. Serum concentrations of Cu in these patients can be influenced by proper nutrition.

A study done by [17] showed another possible explanation: elevated serum copper concentrations have been reported in patients with active colitis and patients taking steroids. An excess of copper may also, by itself, catalyze free radical formation and increase the oxidative stress of the mucosa and thus be of relevance in perpetuating the inflammatory processes in IBD [17]

While, a study done by [22] stated that, the serum level of copper did not differ significantly (P=1) between the UC patients (n=56) and healthy subjects (n=56) and that contradicts the current study.

The present study showed that salivary magnesium was highly significantly decreased in ulcerative colitis patients on two treatment modalities than that in control subjects ($p< 0.001$); this result agrees with a study done by [18] in which study performed in 2015-2016 on 60 recently diagnosed UC patients, showed that UC patients have significantly lower Mg levels compared to healthy individuals.

The result of this study agrees with a study done in [23], the investigation of magnesium hair concentration patterns in an adult population of IBD patients, and noticed a significantly lower magnesium concentration in UC patients. Magnesium levels appear to be modified in IBD patients, which suggests it either plays a primary role in disease pathophysiology or results from the disease's evolution. Magnesium could be used in predictive models for clinical/subclinical disease activity. Moreover, magnesium supplementation may improve IBD evolution and sleep quality for patients with a deficit of this mineral [23].

In a study of 46 IBD patients by [19], the serum Mg level of the patients was lower than that of the controls [19], which is consistent with the current study. It is also consistent with the study done by [20], who claimed that Mg levels are lower in IBD patients than in healthy people [20].

A study conducted in [21] reported that 72% of Crohn's disease patients had micronutrient deficiency, and about 10% of Crohn's disease patients had subnormal serum levels of magnesium [21].

Study limitations

In this study, the nutritional status of IBD patients was not assessed, and there was no data about the nutritional background of the subjects. Moreover, it did not record the extension of the disease, which could affect the nutritional status of subjects.

CONCLUSION

The present study showed that UC patients have significantly lower saliva Zn and Mg levels than healthy individuals. However, salivary Cu in UC patients was higher than in control individuals. Furthermore, this study found that the mean levels of salivary Zn and salivary Mg were significantly lower in UC patients on monotherapy than patients on combination. In contrast, the mean salivary copper level was significantly higher in UC patients on monotherapy.

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