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The Incidence and Risk Factors of Refeeding Syndrome-like Hypophosphatemia in Inflammatory Bowel Disease: A Preliminary Study

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ABSTRACT

Background & Aims: Refeeding syndrome (RFS) is defined by the presence of acute electrolyte disturbances, including hypophosphatemia. Underlying disease(s), malnutrition and hospitalisation are known risk factors for RFS. It can occur in patients with inflammatory bowel disease (IBD). We aimed to determine the frequency of hypophosphatemia and the relationship between hypophosphatemia, disease severity and nutritional status in hospitalized patients with IBD.

Methods: This study was performed prospectively in hospitalized adult patients for the treatment of IBD in a tertiary-care hospital. Disease severity was assessed using Truelove and Witts score for ulcerative colitis (UC) and Crohn's Disease Activity Index for Crohn's disease (CD). Nutritional status was determined using Subjective Global Assessment (SGA). Serum phosphate concentration was recorded for first 7 days after hospitalization, and less than 0.65 mmol/l was defined as hypophosphatemia.

Results: Fifty participants (33 with UC and 17 with CD) were included in the study. The mean age of the study sample was 43.4±14.9 years, of which 64% were male. A total of 8.8% of patients with UC and 37.5% of patients with CD had severe (>moderate) disease upon study admission. Seventeen patients (34%) were malnourished. During the 7 study days, 23 participants (46%) had at least one episode of hypophosphatemia. Serum phosphate concentration was significantly and moderately correlated with serum potassium concentration in both the patients and the hypophosphatemia group on study day 3 ($p<0.05$). Multivariate logistic regression analysis showed that the presence of malnutrition [odds ratio (OR) = 3.64, 95% confidence interval (CI): 1.52-5.58, p=0.008), the administration of parenteral nutrition (OR=2.91, 95%Cl: 1.37-4.63, p=0.015), and severe IBD (OR=1.74, 95%CI: 1.03-3.42, p=0.020) were associated with hypophosphatemia.

Conclusions: Approximately half of the participants exhibited at least one instance of hypophosphatemia during the study period. Hypophosphatemia was found to be associated with malnutrition, parenteral nutrition, and severe disease in patients with IBD requiring hospitalization.

Key words: Crohn's disease – malnutrition, – refeeding hypophosphatemia – ulcerative colitis.

Abbreviations: CD: Crohn's disease; CDAI: CD activity index; CI: confidence interval; IBD: inflammatory bowel disease; NICE: National Institute for Health and Clinical Excellence; OR: odds ratio; RFS: refeeding syndrome; RH: refeeding hypophosphatemia; SD: standard deviation; SGA: Subjective Global Assessment; UC: ulcerative colitis.

INTRODUCTION

Refeeding syndrome (RFS) is defined by the presence of acute electrolyte abnormalities, including hypophosphatemia, hypopotassemia, or hypomagnesemia, fluid disturbances, and various organ/system dysfunctions resulting from the transition from catabolic to anabolic reactions. It may develop in patients with malnutrition and/or reduced food intake when feeding is resumed after prolonged starvation [1-3]. Refeeding syndrome can occur in individuals fed orally (regular diet), enterally (enteral tube feeding), or parenterally [4, 5]. Additionally, the pathogenesis of RFS is thought to be compatible with hypophosphatemia; thus, the term refeeding hypophosphatemia is often used. Furthermore, serum phosphate level is a useful marker that can be easily measured to identify RFS [6].

Inflammatory bowel disease (IBD), two primary forms of ulcerative colitis (UC) and Crohn's disease (CD), are

chronic inflammatory disorders of the gastrointestinal tract. An inflammatory response that initiates catabolism in IBD creates an anorexigenic effect [7]. Inflammatory bowel disease is frequently accompanied by increased energy requirements, which may be attributed to hyper-catabolism. This is frequently accompanied by a reduction in food intake, which may be attributed to postprandial pain, diarrhea or anorexia, intestinal malabsorption and maldigestion due to bowel resection or bypass, and steroid therapy [8]. Consequently, they are prone to malnutrition, which is influenced by the activity, duration, and extent of IBD [7, 9]. Malnutrition has been reported in up to 70% and 38% of patients with IBD in the active and remission stages, respectively [10-12]. The long-term starvation and high malnutrition risk associated with IBD suggest that patients may be at risk for RFS [13]. Additionally, refeeding hypophosphatemia has been observed even after 48 hours of short-term fasting [14]. Currently, there is a paucity of data on RFS in IBD [15], with only a few case reports [16, 17] indicating that patients with IBD may develop RFS.

This study aimed to determine the incidence of hypophosphatemia, the relationship between hypophosphatemia and disease severity, and the nutritional status of IBD patients requiring hospitalization.

METHODS

Study Design and Participants

The prospective study was conducted at the gastroenterology clinic of a tertiary care hospital in Department of Medicine, Division of Intensive Care, Erciyes University School of Medicine, Kayseri, Turkey. Ethical approval was obtained from the local Ethics Committee. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008. Prior to the commencement of the study, written informed consent was obtained from all participants.

The study inclusion criteria were as follows: age ≥ 18 years, expected hospitalization for more than 48 hours due to the diagnosis of UC or CD in the gastroenterology clinic. Patients with chronic renal failure (glomerular filtration rate (GFR) < 60 ml/min) and pregnant women were excluded.

Participants were observed for the first seven days following their admission to the hospital for treatment.

Data Collection

Data on age, gender, body mass index, and reason for hospital admission of study participants were collected at baseline (hospital admission). The severity of the disease was determined using the Truelove and Witts score [18] for patients with UC and the Crohn's Disease Activity Index (CDAI) score [19] for patients with CD. At the time of admission to the study, the nutritional status of each subject was evaluated by a clinical dietitian using the Subjective Global Assessment (SGA) [20]. Nutritional data pertaining to the route of nutrition [oral (regular diet), enteral tube feeding, or parenteral nutrition] and daily energy intake were recorded for each participant during the study period. A food consumption record was compiled by dietitians for patients receiving a regular diet, detailing the food and beverages consumed daily. Furthermore, the administration of oral nutritional supplements was documented. The nutritional data were analyzed using the Nutrition Information System (BeBis) Software program (EBISpro for Windows, Stuttgart, Germany; Turkish version BeBiS, utilising data from the Bundeslebensmittelschlüssel 11.3 database and other sources), which is specific to the Turkish population. The daily energy requirement of patients was calculated in accordance with the European Society for Clinical Nutrition and Metabolism Guideline for IBD [21].

Serum phosphate, magnesium, potassium, and albumin concentrations were measured daily for 7 days. In the clinical setting, serum phosphorus levels were routinely measured at 7 a.m. in patients who were fasting. Hypophosphatemia was defined as a reduction in serum phosphate levels to below 0.65 mmol/L following the initiation of nutritional support, as previously described [2, 22]. Hypomagnesemia (serum magnesium level <0.70 mmol/L), hypopotassemia (serum potassium level <3.5 mmol/L), and hypoalbuminemia (serum albumin concentration < 3.5 mg/dl) were described [23].

At the time of admission to the study, the risk of RFS was assessed evaluated in accordance with the criteria set forth by the National Institute for Health and Clinical Excellence (NICE) criteria [24].

Statistical Analysis

All data were analyzed using the SPSS software (version 26.0). Continuous variables were expressed as mean ± standard deviation (SD) and median (minimum-maximum) according to normal distribution using the Shapiro-Wilk test. Categorical variables were presented as absolute numbers with percentages. For continuous variables, differences between the two groups were assessed using the independent t-test or Mann Whitney U-test. Categorical variables were compared using the chi-squared test. The correlation between two variables was analyzed using Spearman's correlation analysis (Spearman rho), with results classified as follows: negligible (less than 0.2), weak (0.2 to 0.4), moderate (0.4 to 0.6), strong (0.6 to 0.8) or very strong (0.8 to 1.0). In the multivariate analysis, disease severity was classified as severe according to the Truelove and Witts score for UC patients and as moderate to severe or severe according to the CDAI for CD patients. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 73 patients were assessed for eligibility, and 50 were included in the study (Fig. 1). Of the patients, 64.0% were male. The mean age of the patients was 43.4 ± 14.9 years. The mean BMI was 24.3 ± 4.40 kg/m^2. A total of 66% of the study sample consisted of patients with UC, and the rest were patients with CD. According to the Truelove Witts score, 64.7% of the participants with UC exhibited moderate disease activity, 26.5% exhibited mild disease activity, and 8.8% exhibited severe disease activity. Of the patients with CD, 43.8% were in remission, 25.0% had moderate to severe disease, 18.8% had moderate disease, and 12.5% had severe disease (Table I).

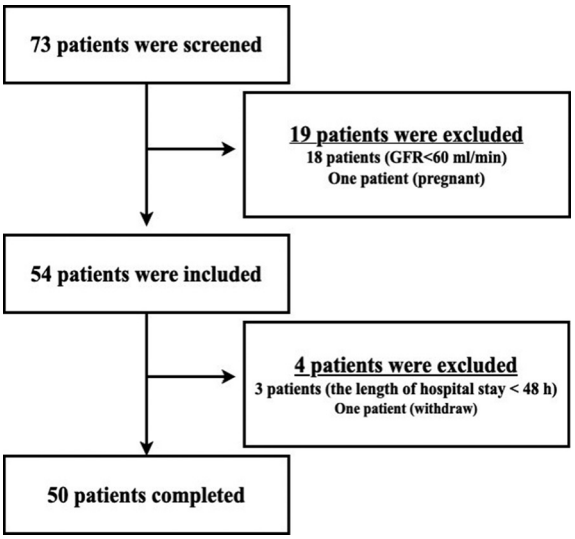

Fig. 1. The flow chart of the study.

A total of 15 participants (30.0%) were identified as being at risk of malnutrition, while 17 patients (34.0%) were classified as malnourished according to the SGA.

A total of 27 participants (54%) received a regular diet with or without oral nutritional supplements, while 30% and 14% received parenteral nutrition and enteral tube feeding, respectively. Only one patient did not receive any nutritional intervention during the study period (Table II).

During the 7 study days, 23 participants (46%) experienced at least one hypophosphatemia and were defined as the hypophosphatemia group. The highest incidence of hypophosphatemia was observed on the fifth study day, with seven patients (14.0%) affected (Fig. 2).

In hypophosphatemia group, serum phosphate concentration decreased during first 4 days and reached to lowest serum phosphate level on day 4 (0.71±0.15 mmol/l) and Day 5 (0.71±0.25 mmol/l) after study admission. Then, it rose modestly until day 7 (Fig 3).

Table I. Patients' clinical characteristics

	Total (n=50)	Hypophosphatemia (n=23)	No - hypophosphatemia (n=27)	p
Demographic and clinical assessment				
Age (years), ± SD	43.4 ± 14.9	39.6 ± 13.5	46.6 ± 15.5	0.097
Gender, n (%)	32 (64)	18 (78.2)	14 (51.9)	051
Male	18 (36)	5 (21.8)	13 (48.1)	
Female				
BMI (kg/m^2), ±SD	24.3 ± 4.40	22.5 ± 4.02	25.8 ± 4.10	0.006
Anatomic location of disease, n (%)				
Ulcerative colitis	33 (66)	15 (65)	18 (67)	
Left-sided colitis	10 (20)	4 (17)	6 (22)	
Distal	12 (24)	5 (22)	7 (26)	
Pancolitis	3 (6)	2 (9)	1 (4)	
Proctitis	2 (4)	1 (4)	1 (4)	
Remission	6 (12)	3 (13)	3 (11)	0.544
Crohn's disease	17 (34)	8 (35)	9 (33)	
İleal				
Colonic	1 (2)	0	1 (4)	
İleacolonic	7 (14)	3 (13)	4 (15)	
Fistulizing	5 (10)	3 (13)	2 (7)	
Remission	2 (4)	2 (9)	0	
	2 (4)	0	2 (7)	
Truelove Witts Score (n=33)				0.459
Mild	9 (36.4)	2 (13.3)	7 (38.8)	
Moderate	21 (42.4)	11 (73.4)	10 (55.6)	
Severe	3 (21.2)	2 (13.3)	1 (5.6)	
CDAI (n=17)				0.126
Remission	7 (41.3)	2 (25.0)	5 (55.6)	
Mild to moderate	3 (17.6)	1 (12.5)	2 (22.2)	
Moderate to severe	4 (23.5)	3 (37.5)	1 (11.1)	
Severe	3 (17.6)	2 (25.0)	1 (11.1)	
Laboratory parameters				
Baseline serum potassium level (mmol/L), ±SD	4.4 ± 0.53	4.4 ± 0.59	4.4 ± 0.47	0.946
Baseline serum magnesium level (mmol/L), ±SD	0.82 ± 0.08	0.84 ± 0.09	0.81 ± 0.68	0.127
Baseline serum albumin level (g/L), ±SD	3.84 ± 0.63	3.76 ± 0.78	3.92 ± 0.47	0.365
Baseline serum CRP level, min-max	29.2 (0.3-109.2)	29.1 (0.5-87.9)	29.6 (0.3-109.2)	0.673
Length of hospital stay (day), min-max	12.0 (3.0-43.0)	14.0 (3.0-43.0)	10.0 (3.0-20.0)	0.453

BMI: body mass index; CDAI: Crohn's disease activity index; CRP: C reactive protein; SD: standard deviation.

Table II. Patient nutritional parameters

	Total (n=50)	Hypophosphatemia (n=23)	No - hypophosphatemia (n=27)	p
SGA, n (%)				0.001
Well-nourished	18 (36.0)	5 (21.7)	13 (48.1)	
At malnutrition risk	15 (30.0)	4 (17.4)	11 (40.7)	
Malnourished	17 (34.0)	14 (60.9)	3 (11.2)	
Type of nutrition*, n (%)				0.006
Nill by mouth	1 (2)	1 (4)	0	
Regular diet	27 (54)	7 (30)	20 (74)	
Enteral tube feeding	7 (14)	3 (13)	4 (15)	
Parenteral nutrition	15 (30)	12 (53)	3 (11)	
Daily energy requirement (kcal/day), ±SD	1847.1 ± 177.37	1783.3 ± 156.18	1925.0 ± 174.36	0.005
Baseline daily energy intake, (kcal/day), ±SD	1286.2 ± 565.61	1213.1 ± 648.20	1348.5 ± 488.52	0.416
Daily mean adequacy of energy target, (%)				
Day 1	70.2	62.9	76.3	0.108
Day 2	69.7	64.9	73.7	0.302
Day 3	71.4	65.1	76.8	0.053
Day 4	73.3	68.2	77.5	0.126
Day 5	74.4	71.3	78.9	0.219
Day 6	75.8	74.4	79.3	0.166
Day 7	76.1	74.6	78.2	0.263

*It shows baseline type of nutrition.

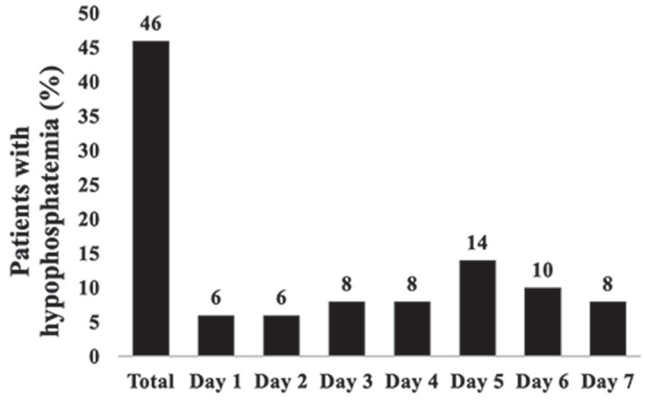

Fig. 2. The distribution of patients with hypophosphatemia over 7 study days. Total bar shows that patients had at least one episode of hypophosphatemia at any time during the study period.

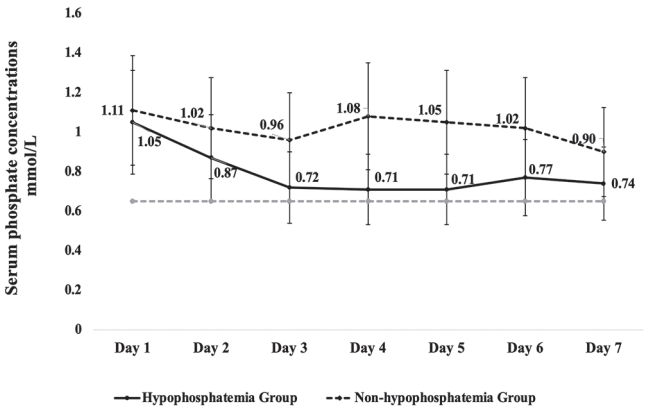

Fig. 3. Serum phosphorus levels during the study period. Data shows as median (25^{th}-75^{th} quartile). Grey indicates lower reference value of serum phosphorus value (0.65 mmol/L).

In addition, 25 patients were at risk of RFS according to the NICE criteria. The presence of hypophosphatemia was associated with RFS risk (p=0.011) (Supplemental file).

At baseline, only one patient had hypopotassemia and two patients had hypomagnesemia. The serum potassium and magnesium concentrations during the 7 study days are shown in Fig. 4. Serum potassium level declined on day 3 (4.17 ± 0.56 mmol/l) and remained lower value at day 4 (4.26 ± 0.56 mmol/L) and day 5 (4.22 ± 0.59) compared to non-hypophosphatemia group, but not significantly. The serum magnesium level decreased slightly on day 4 (0.78 ± 0.12 mmol/L), then rose on day 5 (0.86 ± 0.05 mmol/L). However, the hypophosphatemia group had lower magnesium levels than the non-hypophosphatemia group during the study period, although this was not a statistically significant difference (Fig. 4).

Serum phosphate concentration was moderately correlated with serum potassium concentration in all patients on day 3 (rho=0.488, p=0.003). In addition, there was a moderate correlation between serum phosphate and serum potassium levels in the hypophosphatemia group on day 3 (rho=0.517, p=0.019) (Fig. 5). In the non-hypophosphatemia group, serum phosphate levels were moderately correlated with serum potassium levels on the 6th study day (rho=0.411, p=0.033) (Supplementary file).

The Chi-Square test demonstrated that malnourished participants according to SGA experienced significantly more hypophosphatemia episodes than the other patients (p=0.001). While 53% of the hypophosphatemia group received parenteral nutrition, 74% of the non-hypophosphatemia group was fed a regular diet. In addition, one participant did not receive any nutritional support and demonstrated hypophosphatemia. The mean daily energy requirement of the non-hypophosphatemia group was found to be higher than that of the hypophosphatemia group (p=0.005).

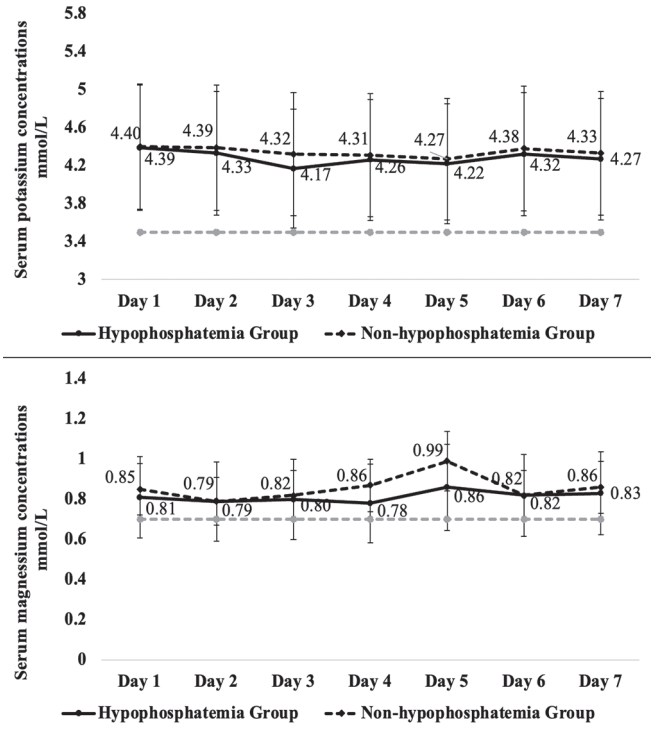

Fig. 4. Serum potassium and magnesium concentrations during study follow-up. Data shows as median (25th-75th quartile) of serum potassium (above) and magnesium (below) value. Grey indicates lower reference value of serum potassium (3.5 mmol/L) and magnesium (0.70 mmol/L) levels.

The hypophosphatemia group achieved approximately 62-65% of their daily energy requirement in the first three study days, while the non-hypophosphatemia group reached 73-76% of their daily energy requirement ($p > 0.05$) (Table II).

In Table III, multivariate logistic regression analysis showed the presence of malnutrition based on SGA (odds ratio (OR) = 3.64, 95% confidence interval (CI): 1.52-5.58, p=0.008), parenteral nutrition on study admission (OR=2.91, 95%Cl: 1.37-4.63, p=0.015), and severe IBD (OR=1.74, 95%Cl: 1.03-3.42, p=0.020).

DISCUSSION

To the best of our knowledge, this is the first prospective study to identify the incidence of hypophosphatemia in patients with IBD. Our results demonstrated that 46% of adult inpatients with IBD developed at least one episode of hypophosphatemia within seven days of hospital admission. The most common occurrence of hypophosphatemia was observed in seven patients (14% of the study sample) on the fifth study day. The participants exhibited the lowest phosphate concentrations on both the 4th and 5th study days. A significant moderate correlation was observed between serum phosphate and serum potassium concentrations in both the patients and the hypophosphatemia group on day 3. Hypophosphatemia was significantly associated with malnutrition, parenteral nutrition and severe IBD.

Approximately 50% of our study population developed at least one hypophosphatemia during the 7 study days. There are only two case reports of hypophosphatemia in the literature. In a case report, 21 years old patient with CD had persistent bloody diarrhea (7-10 times/day) during the last 15 days and history of 20 kg weight loss throughout the last month. He received enteral nutrition via nasogastric tube and experienced hypophosphatemia (serum phosphate level: 0.5 mg/dL, reference range: 2.5-4.5 mg/dL) within 72 hours after refeeding. Phosphate replacement was administered, and the serum phosphate level increased to the reference range [10]. Furthermore, a 14-year-old girl with CD who was receiving polymeric enteral nutrition developed hypophosphatemia on the fifth hospital day [11]. Indeed, the data presented here appear to be cause for concern, particularly in the context of patients with IBD.

During our study, one patient exhibited hypopotassemia at baseline, while two others displayed hypomagnesemia. A patient with hypopotassemia at baseline exhibited hypophosphatemia during the follow-up period. Following the commencement of feeding, serum potassium and magnesium levels are frequently affected, with low initial levels being considered a sign of hypophosphatemia [25]. In this study, serum phosphate concentration was found to be correlated with serum potassium concentration in both the hypophosphatemia

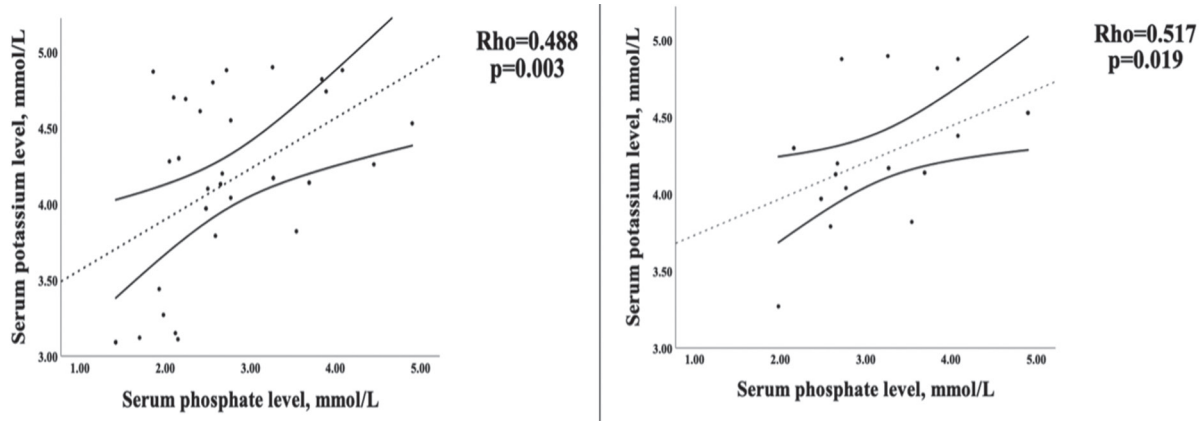

Fig. 5. The correlation between serum phosphate and serum potassium value. It shows the relationship between serum phosphate and serum potassium concentrations on day 3 in all patients (left) and the hypophosphatemia group (right) by Spearman correlation analysis.

Table III. Multivariate logistic regression analysis of hypophosphatemia (n=50)

	Odds ratio	95% Cl	p-value	
			Lower	Upper
Presence of malnutrition[1]	3.64	1.52	5.58	0.008
The administration of parenteral nutrition	2.91	1.37	4.63	0.015
Severe disease[2]	1.74	1.03	3.42	0.020

[1] Malnutrition was diagnosed by SGA; [2] It was considered severe according to Truelove and Witts score or moderate-severe and severe according to CDAI score.

group and in all patients on day 3. It is postulated that low serum potassium levels may be a contributing factor in the development of hypophosphatemia. Furthermore, our findings are in accordance with the conclusions of a prospective cohort study that identified hypomagnesemia as an independent predictor of hypophosphatemia [26].

During the initial three study days, the non-hypophosphatemia group reached approximately 73-76% of their daily energy requirements, whereas the hypophosphatemia group achieved approximately 62-65% of their daily energy requirements. An inflammatory response that is part of IBD may cause an anorexigenic effect [7]. We believe that this decreased energy intake may have contributed to the decrease in serum phosphate levels on the 4th and 5th study days.

In our cohort, malnutrition (OR=3.64), parenteral nutrition (OR=2.91), and severe IBD (OR=1.74) were risk factors for hypophosphatemia. In total, 36% of the participants were malnourished. Similarly, two studies found that 37.6% and 38.1% of the inpatients with IBD had malnutrition by SGA [27, 28]. While 60.9% of the hypophosphatemia group had malnutrition, 48.1% of the non-hypophosphatemia group were well nourished. As malnutrition increased, the frequency of hypophosphatemia increased significantly. This finding is consistent with the fact that malnutrition and hypophosphatemia may be closely related [29, 30].

Most participants with hypophosphatemia (53%) received parenteral nutrition, whereas 74% of patients without hypophosphatemia were fed a regular diet. In our clinical setting, patients receiving parenteral nutrition were offered an all-in-one parenteral solution contains approximately 8.5 mmol phosphate, 16 mmol potassium, and 2.2 mmol magnesium in one liter without additional phosphate, potassium, and magnesium. In case of hypophosphatemia, study participants were given replacement with 0.3 mmol/kg/day PO4 (as K3PO4) over 8–12 hours [31]. Parenteral nutrition provides all nutrients that directly participate in the blood circulation system and may cause hyperinsulinemia. This switch can result in rapid cellular uptake of electrolytes (phosphate, potassium, and magnesium) [32]. Oral and/or enteral nutrition can protect against hyperinsulinemia thanks to its incretin effect.

Our cohort generally consisted of patients with mild-to-moderate disease. However, 2 of 3 patients with severe UC and 5 of 7 patients with moderate-to-severe CD demonstrated RFS. Similarly, most patients in the non-hypophosphatemia group had mild disease. Severe disease was a risk factor of hypophosphatemia in patients with IBD. There are two possible reasons for this. First, phosphorus is absorbed in the intestine, and the bowel affected by IBD may pose a danger to hypophosphatemia. Secondly, increased severity of disease may contribute to malnutrition, resulting in hypophosphatemia [8, 15]. We believe that the severity of the disease should be taken into consideration when assessing hypophosphatemia.

Refeeding syndrome-like hypophosphatemia may cause many adverse clinical outcomes such as prolonged hospitalization, increased morbidity, and mortality. In our study, the length of hospital stay was longer in the patients with refeeding hypophosphatemia (RH), non-significantly. Coskun et al. [33] reported a longer ICU stay in critically ill patients with RH than in those without RH. Patients with IBD may benefit from treatment with early diagnosis of RFS like hypophosphatemia.

Our study has some limitations. It was conducted at a single center and had a small sample size. The incidence of hypophosphatemia in patients with IBD should be evaluated using larger samples, including different nutrition types, short/long-term starvation, and disease severity. In addition, this study included most participants with active IBD. The data should be compared to those of participants in the remission stage of IBD. We did not measure urinary phosphate excretion and calculated the TmP/GFR value of participants. Therefore, the data should be confirmed by a comprehensive assessment including measurement of urinary phosphate excretion, calculating TmP/GFR, and serum CRP levels in larger samples.

Consequently, our data showed that IBD-patients had a high incidence of hypophosphatemia in the first 7 days after hospitalization. Malnutrition, parenteral nutrition, and the presence of severe IBD are associated with the development of hypophosphatemia in adult patients with IBD. All inpatients should be closely monitored because RFS may develop even during short-term starvation. Furthermore, hypophosphatemia should be considered as an additional component of comprehensive clinical assessment for IBD.

Conflicts of interest: None to declare.

Authors' contribution: N.T.O., G.C.S., M.A.Y. and K. Gundogan equally contributed to the conception and design of the research. K. Guven contributed to the design of the research. N.T.O. contributed to the acquisition and analysis of the data. N.T.O., S.S.E, G.G.S., and K. Gundogan were involved in statistical analysis of the data. N.T.O. and K. Gundogan contributed to the interpretation of the data. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5502

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