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THE RELATIONSHIP BETWEEN UNDERNUTRITION AND ANEMIA IN ULCERATIVE COLITIS PATIENTS: A CROSS-SECTIONAL STUDY RESULTS

[1] Ivanov Sergei Vitalyevich, [1,2] Uspenskiy Yury Pavlovich, [1] Fominykh Yulia Aleksandrovna, [3]Khoroshilov Igor Evgenyevich

[1]St. Petersburg State Medical University named after I.P. Pavlov. 197022 Russia St. Petersburg, L'va Tolstogo street, 6–8.

[2]St. Petersburg Pediatric Medical University. 194100, St. Petersburg, Litovskaya street, 2.

[3]North-Western State Medical University named after I.I. Mechnikov. 191015, Russia, St.Petersburg, Kirochnaya street, 41

Contact Information: Ivanov Sergei Vitalyevich — PhD, Associate Professor of Department of Internal Diseases of Dentistry Faculty of St. Petersburg State Medical University named after I.P. Pavlov. E-mail: tervestnik@mail.ru

SUMMARY. *Background*. The anemia and the undernutrition are frequent ulcerative colitis (UC) complications, but the impact of undernutrition to anemia isn't assessed from point of view of practical approach. Our objective is to assess relationship between of the undernutrition and the anemia in UC patients. *Methods*. The cross-sectional retrospective analysis included data from medical records of 80 UC patients. Demographic characteristics, disease behavior, gut involvement extension, immunosupressive therapy applying, laboratory parameters (hemoglobin and total serum protein levels) were collected. Body mass index (BMI) and fat mass were collected retrospectively from bioimpedance analysis data. Anemia was diagnosed retrospectively by WHO criteria: hemoglobin level less than 13 g/dl for male and less than 12 g/dl for female. Substantial fat mass loss was estimated by Tanita reference tables. A binary logistic regression was performed to study the relationship between nutrition status parameters and anemia occurrence adjusted for demographic and disease-associated characteristics. *Results*. Prevalence of anemia in the sample was 40.0%. In adjusted binary logistic model total serum protein level below 64 g/l and substantial fat mass loss were associated with a high odds of anemia occurrence: OR 5.1 (95% CI 1.5; 17.8) and 8.5 (95% CI 1.1; 63.6) respectively. Adjusted model includes gender, age, disease activity, extent of gut involvement, quantity of relapses from disease beginning and treatment with immunosuppressive medications as confounders. *Conclusion*. We assume undernutrition is one of the causative agents of anemia in UC patients. Findings in the present study could have significant implications for physicians caring for UC patients with anemia and undernutrition.

KEY WORDS: Inflammatory bowel diseases; Ulcerative colitis; Nutritional status; Undernutrition; Fat mass; Total serum protein; Anemia.

ВЗАИМОСВЯЗЬ МЕЖДУ НЕДОСТАТОЧНОСТЬЮ ПИТАНИЯ И АНЕМИЕЙ ПРИ ЯЗВЕННОМ КОЛИТЕ: РЕЗУЛЬТАТЫ ПОПЕРЕЧНОГО ИССЛЕДОВАНИЯ

[1]Иванов Сергей Витальевич, [1,2]Успенский Юрий Павлович, [1]Фоминых Юлия Александровна, [3]Хорошилов Игорь Евгеньевич

[1] Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова. 197022, Санкт-Петербург, ул. Льва Толстого, д. 6–8.

[2]Санкт-Петербургский государственный педиатрический медицинский университет. 194100, Санкт-Петербург, Литовская ул., д. 2.

[3]Северо-западный государственный медицинский университет имени И.И. Мечникова. 191015, Россия, г. Санкт-Петербург, ул. Кирочная, д.41

Контактная информация: Иванов Сергей Витальевич — кандидат медицинских наук, доцент кафедры внутренних болезней стоматологического факультета. 197022, Санкт-Петербург, ул. Льва Толстого, д. 6–8. E-mail: tervestnik@mail.ru

РЕЗЮМЕ. Анемия и недостаточность питания являются частыми осложнениями язвенного колита (ЯК), но влияние недостаточности питания на развитие анемии с практической точки зрения не оценивалось. *Цель исследования* — оценить взаимосвязь между недостаточностью питания и анемией у пациентов с ЯК. *Материалы и методы*. Проведено поперечное ретроспективное исследование, в которое были включены данные из медицинских карт 80 пациентов с ЯК. Были проанализированы демографические характеристики пациентов, особенности течения заболевания, степень поражения толстой кишки, применение иммуносупрессивной терапии, лабораторные показатели (уровни гемоглобина и общего сывороточного белка). Сведения об индексе массы тела (ИМТ) и массе жировой ткани были собраны ретроспективно на основании результатов биоимпедансного анализа состава организма пациентов, который проводился за время их пребывания в клинике. Анемия была диагностирована ретроспективно согласно критериям ВОЗ: уровень гемоглобина менее 130 г/л для мужчин и менее 120 г/л для женщин. Значительная потеря массы жира была оценена с помощью справочных таблиц Tanita. Для оценки взаимосвязи между параметрами состояния питания и частотой возникновения анемии с учетом демографических и связанных с заболеванием характеристик был проведен бинарный логистический регрессионный анализ. *Результаты*. Распространенность анемии в изучаемой популяции пациентов составила 40,0%. В скорректированной бинарной логистической модели уровень общего сывороточного белка ниже 64 г/л и значительная потеря массы жира были связаны с более высокой вероятностью возникновения анемии: отношение шансов 5,1 (95% ДИ 1,5; 17,8) и 8,5 (95% ДИ 1,1; 63,6) соответственно. Помимо показателей нутриционного статуса, скорректированная модель включала в себя следующие факторы: пол, возраст пациентов, активность заболевания, степень поражения кишечника, количество рецидивов от начала заболевания и факт лечения иммунодепрессивными препаратами. *Выводы*. Выдвинуто предположение о том, что недостаточность питания является одним из факторов развития анемии у пациентов с ЯК.

КЛЮЧЕВЫЕ СЛОВА: воспалительные заболевания кишечника; язвенный колит; нутриционный статус; недостаточность питания; жировая масса; общий белок; анемия.

INTRODUCTION

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis (UC), are severe chronic idiopathic disorders of gastrointestinal tract, that present with periods of relapses and remissions throughout their clinical course [28, 26]. Anemia is one of the most fre-

quent complications in IBD [1, 15, 11]. From the practical point of view, anemia contributes to patients' low quality of life, particularly because of its negative impact on the feeling of wellbeing, cognitive function, potentially limiting their ability to perform social and physical activities [33]. In addition, anemia in IBD patients is a significant predictor of increased risk of hospitalization and even increased patient mortality [5, 9, 17, 3].

The reported prevalence of anemia in patients with IBD varies from 6% to 74% [7]. One of causes of wide variability of anemia prevalence is a heterogeneity of population of patients. In different studies hospitalized and outpatient cases examined separately or mutually [27].

Table 1

Prevalence of anemia in UC patients in different populations

Population	In-patients	Out-patients
Europe	15-27%	
Sweden	35%	5%
Switzerland	60%	18%
Brasil	-	18%
Russian Federation	6-14%	-

Prevalence of anemia in UC in different populations presented in Table 1 [7, 23, 30, 25].

The anemia in IBD is likely to be multifactorial in origin, frequently being the result of a combination of iron deficiency (the major cause) and anemia of chronic disease [27, 10, 24, 31, 32]. In some cases, anemia may also be induced by sulfasalazine, thiopurines, hemolysis, and myelodysplastic syndrome [10].

On the other hand IBD is frequently associated with undernutrition. Up to 75% of patients with an active phase of IBD suffer from weight loss and hypoalbuminemia. Undernutrition with muscle and fat mass loss is more frequent in Crohn's disease than in UC and is usually restricted to the active phase of disease [2, 12]. The presence of undernutrition has been linked to adverse outcomes [6, 8].

The etiology of malnutrition in patients with UC is multifactorial and includes poor nutritional intake due to postprandial pain, diarrhea or anorexia, malabsorption and maldigestion due to either active disease, as well as protein loss through the bowel and metabolic stress associated with both inflammation and steroid therapy [21, 19].

As noted in ESPEN guidelines on enteral nutrition in gastroenterology, the information regarding undernutrition in UC derives mainly from case reports and there are no epidemiological studies that would allow estimation of the prevalence of underweight and weight loss in UC patients. Complex specific information on alterations of body composition in UC, i.e. relative changes in muscle mass and fat mass, are not available. Studies reported trace elements deficiencies and vitamins deficiencies leading to anemia in UC patients [18].

As in a wide variety of diseases, including cancer, heart failure, renal failure, chronic obstructive pulmonary disease and HIV, in IBD both alterations in appetite and body weight loss occur [2]. Decreased appetite and involuntary weight loss are common occurrences in chronic disease and have a negative impact on quality of life and mortality. Equal weight loss comes from fat and lean mass isn't infrequent condition in IBD patient. This would lead to tissue losses of both fat (depletion of energy stores) and muscle tissue (functional decline). Conditions and risk factors that lead to cachexia and inadequate nutrition may independently lead to increased mortality [4, 16].

It is clearly that decreased food intake, catabolic activity due to inflammation and steroid therapy contributes to nutritional status changes. But the relationship between nutrition status and hemoglobin level decline is neglected and requires detailed consideration from practical approach. Protein and energy deficiency accompanies undernutrition in UC patients, so pathophysiological association between anemia and undernutrition is potentially possible. On the other hand, essentially all circulating serum iron normally is bound to transferrin, whereas transferring decrease rapidly in undernutrition condition [2].

Thus the possible mechanism of pathogenic association between undernutrition and anemia presented in Figure 1.

The aim of study was to evaluate the relationship between undernutrition and anemia among patients with ulcerative colitis adjusted for confounding factors affecting hemoglobin level.

MATERIALS AND METHODS

Study design

A retrospective, cross-sectional study was conducted among patients hospitalized to gastroenterology department of North-Western state medical university (St. Petersburg, Russia) from 2011 until 2015.

Patients and data collection

Study data was exacted from patient's medical records. Demographic characteristics, disease behavior, gut involvement extension, ap-

plying of immunosupressive therapy, laboratory parameters were collected. Total body mass, body mass index (BMI) and fat mass were collected retrospectively from bioimpedance analysis data.

Anemia was diagnosed retrospectively by WHO criteria: hemoglobin level less than 13 g/dl for male and less than 12 g/dl for female. Fat mass loss was estimated by Tanita reference tables (Table 2) [13].

Initial review of medical records identified 141 potentially eligible patients. After verification of necessary data the final sample for statistical analysis was formed (Figure 2).

Table 2

Criteria of fat mass loss

Age	Fat mass percentage	
	Males	Females
20–39	<7%	<21%
40–59	<10%	<23%
60–79	<12%	<24%

Statistical analysis

The continuous variables were expressed as medians with upper and lower quartiles. The categorical variables were expressed as numbers with percentages. Bivariate analyses were performed using Pearson's chi squared tests.

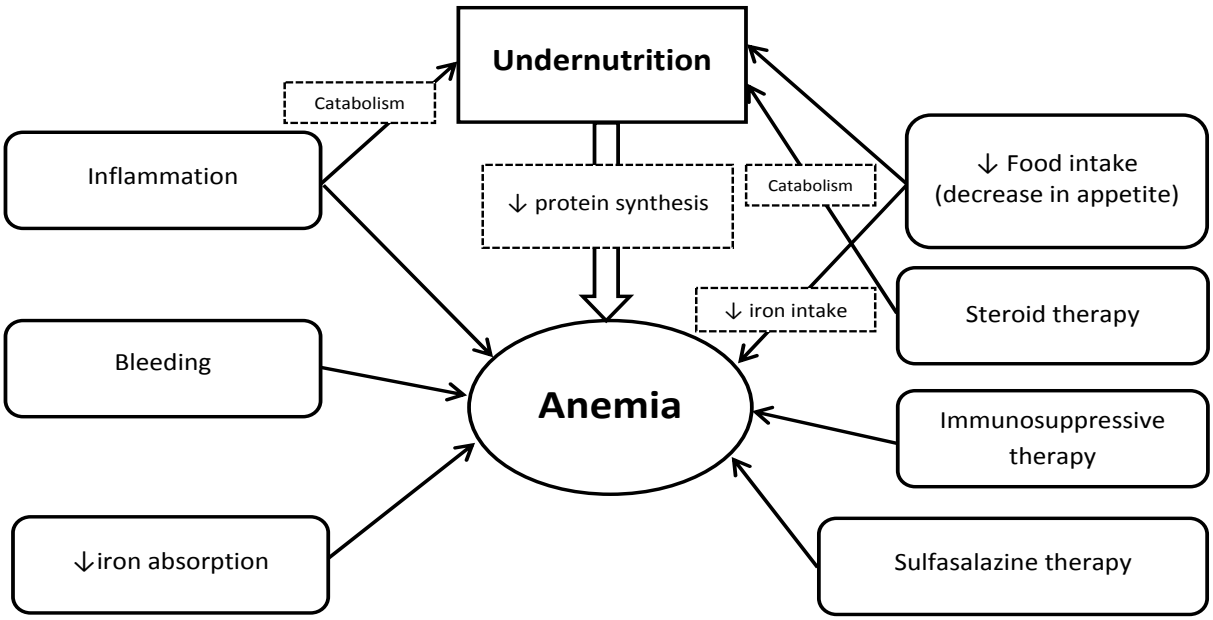


Fig. 1. Possible mechanism of pathogenic association between undernutrition and anemia.

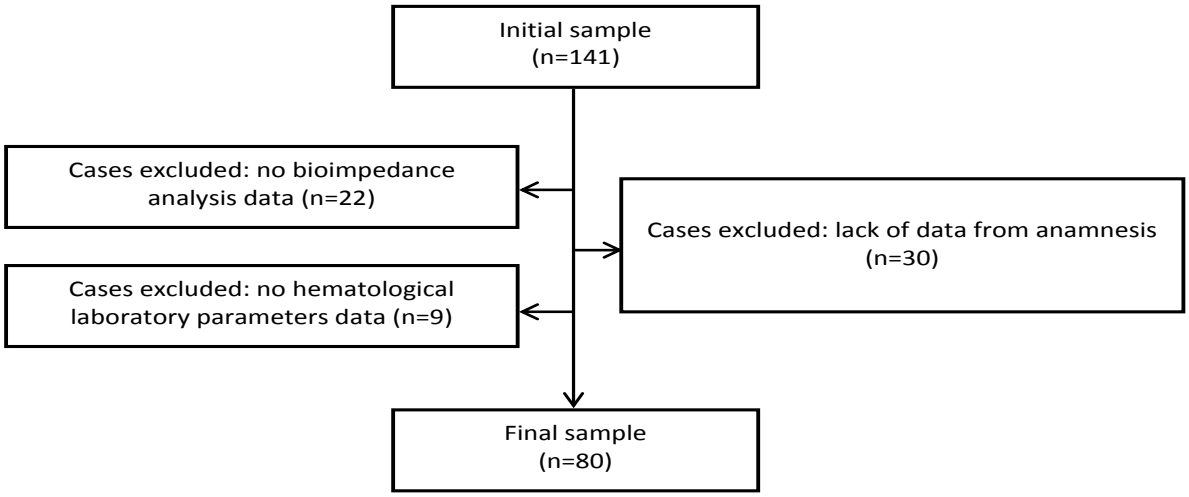


Fig. 2. Final sample forming.

The studied outcome was the case of anemia. Confounders were gender, age, disease activity, extent of gut involvement, quantity of relapses from disease beginning and immunosuppressive medications treatment. A binary logistic regression was performed to study the association between nutrition status parameters and anemia occurrence adjusted for demographic and disease-associated characteristics. Independent effects of each independent variable on the anemia were assessed. Variables were entered into model by forced entry method. We report crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI). SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical calculations. For all tests, a p value of <0.05 was considered statistically significant.

Table 3

Nutritional, demographic, disease-associated and laboratory data

Variables	N (%)	Median (Q1; Q3)
All	80 (100.0)	
Nutritional status		
BMI, kg/m2		22.1 (19.6; 25.3)
< 18.5 kg/m2	12 (15.0)	
≥ 18.5 kg/m2	68 (85.0)	
Fat mass loss		
Yes	8 (10.0)	
No	72 (90.0)	
Total serum protein, g/l		69 (64; 74)
< 64 g/l	16 (20.0)	
≥ 64 g/l	64 (80.0)	
Hemoglobin, g/dl		129.5 (114.0; 145.0)
Anemia		
Yes	32 (40.0)	
No	48 (60.0)	
Demographic characteristics		
Gender		
Male	51 (63.7)	
Female	29 (36.3)	
Age		34.5 (27.0; 50.8)
Disease-associated characteristics		
Acute disease		
Yes (S1–3)	69 (86.3)	
No (S0)	11 (13.8)	
Extent of gut involvement		
Proctitis and left-sided colitis	40 (50.0)	
Pancolitis	40 (50.0)	
Immunosuppressive therapy		
Yes	20 (25.0)	
No	60 (75.0)	
Quantity of relapses from disease beginning		5 (3; 8)

RESULTS

A total of 80 of UC patients were recruited into the study. Baseline clinical characteristics of patients with UC are shown in Table 3. Majority of the patients were males. 86.3% of patients were admitted to the hospital with acute disease (S1–3 disease behavior), and only 13.8% of patients were into remission phase of UC (S0 disease behavior). Half of patients had pancolitis, others had left-sided colitis and proctitis. Prevalence of anemia in the sample was 40.0%.

Prevalence of anemia across nutritional, demographic, disease-associated and laboratory characteristics is presented in Table 4. In the bivariate analysis results, there were significant association between anemia occurrence and low total serum protein level (p=0.009). There is no significant association between fat mass loss, BMI <18.5 kg/m^2 and anemia in crude analysis.

The results of binary logistic regression are presented in Table 5. Two binary logistic models were fitted. The model 1 includes BMI level bi-

Table 4

Prevalence of anemia stratified by nutritional, demographic, disease-associated and laboratory data

Patients characteristics	Anemia N (%)		p-value
	Yes	No	
All	32 (40.0)	48 (60.0)	
BMI level			0.206
< 18.5 kg/m2	7 (8.8)	5 (6.3)	
≥ 18.5 kg/m2	25 (31.3)	43 (53.8)	
Fat mass losses			0.054
Yes	6 (7.5)	2 (2.5)	
No	46 (57.5)	26 (32.5)	
Total serum protein			0.009
< 64 g/l	11 (13.8)	5 (6.3)	
≥ 64 g/l	21 (26.3)	43 (53.8)	
Gender			0.255
Male	18 (22.5)	33 (41.3)	
Female	14 (17.5)	15 (18.8)	
Acute disease			0.511
Yes (S1–3)	29 (36.3)	40 (50.0)	
No (S0)	8 (10.0)	3 (3.8)	
Extent of gut involvement			0.361
Proctitis and left-sided colitis	14 (17.5)	26 (32.5)	
Pancolitis	18 (22.5)	22 (27.5)	
Immunosuppressive therapy			0.598
Yes	11 (13.8)	9 (11.3)	
No	23 (28.7)	37 (46.3)	

nary variable and total serum protein level binary variable as main independent variables and other variables as covariates. In the model 2 BMI level was replaced by fat mass level binary variable (fat mass loss).

In the model 1 variation in anemia across total serum protein background was remained on significant level after adjustment for covariates. In the model 2, variation in anemia across fat mass losses shifted from non-significant to significant level after adjustment for covariates.

Model 2 was fitted better then model 1 (e.g. Nagelkerke R^2 was 0.238 vs 0.182 respectively), so patients with low body fat percentage had 8.5 times greater odds for belonging to the patients with anemia. Those who had low total serum protein level had 5.6 times greater odds for this one.

DISCUSSION

The results of this first to our knowledge study of relationship between total serum protein level, fat mass loss and hemoglobin level suggest practically significant interaction between nutritional status and anemia. Serum protein level below 64 g/l and fat mass loss were associated with a high frequency of anemia: OR 5.1 (95% CI 1.5; 17.8) and 8.5 (95% CI 1.1; 63.6) respectively.

The results of this study should be interpreted with caution due to its potential limitations. Major limitation of the study was its retrospective design with medical records collection, caused lack of objective laboratory data of disease activity, e.g. C-reactive protein level. Furthermore, the cross-sectional design does not allow making clear inferences about causality. However, most of the studied factors are known to precede the hemoglobin level measurement, such as age, gender, disease behavior etc., potentially interacts with iron metabolism and erythropoiesis. For example, disease severity may both cause of undernutrition and be a result of it, although it has been suggested that this bias is a minor component of hemoglobin level inequalities.

The advantage of study was inclusion both patients with UC relapse (S1–S3) and patients with UC in remission phase (S0). Patients with relapses correspond common in-patient cases category, patients with remission correspond common out-patient cases category. Given that the sample is reasonable representative, the acceptable validity of the nutritional status and the

Table 5

Association between anemia and nutritional, demographic, disease-associated and laboratory data

Patient's characteristics	Crude		Adjusted*			
			Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
BMI level		0.168		0.259	-	-
BMI < 18.5 kg/m2	2.4 (0.7; 8.4)		2.2 (0.6; 8.5)			
BMI ≥ 18.5 kg/m2	reference		reference			
Fat mass loss		0.050	-	-		0.037
Yes	5.3 (0.1; 28.2)				8.5 (1.1; 63.6)	
No	reference				reference	
Total serum protein		0.012		0.010		0.009
< 64 g/l	4.5 (1.4; 14.6)		5.1 (1.5; 17.8)		5.6 (1.5; 20.7)	
≥ 64 g/l	reference		reference		reference	
Acute disease		0.360		0.269		0.153
Yes (S1–3)	1.9 (0.5; 7.9)		2.6 (0.5; 14.1)		3.6 (0.6; 20.9)	
No (S0)	Reference		reference		reference	
Extent of gut involvement		0.362		0.601		0.730
Proctitis and left-sided colitis	Reference		reference		reference	
Pancolitis	1.5 (0.6; 3.7)		1.3 (0.4; 4.0)		1.2 (0.4; 4.5)	
Immunosuppressive therapy		0.599		0.697		0.744
Yes	1.3 (0.5; 3.7)		1.3 (0.4; 4.4)		1.2 (0.3; 4.5)	
No	reference		reference		reference	

* adjusted for age, disease acuteness, extent of gut involvement, immunosuppressive therapy and quantity of relapses from disease beginning.

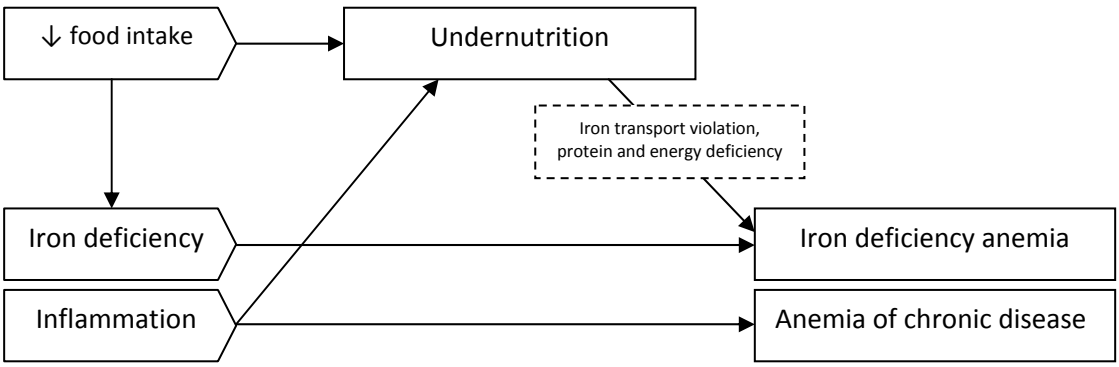


Fig. 3. Directed acyclic graph of possible causal structure of anemia occurrence in UC patients with considering of undernutrition condition.

inclusion of many potential confounding factors, we feel confident that our findings can be generalized to the Russian adult UC patients.

Nevertheless, pathogenic mechanism of relationship between fat mass loss, total serum protein decline and low hemoglobin level isn't quite clear. As is known, fast progressing malnutrition in IBD patients is characterized by transferrin and albumin decreasing with lesser changes in body composition [2]. The rapid decrease of transferrin quantity potentially results to iron transport disruption and anemia worsening.

On the other hand, the reduction of fat mass indicatives the exhaustion of body energy storage on the background of active inflammation and catabolism may indirectly reduce the activity of synthetic processes, e.g. synthesis of hemoglobin and erythropoiesis.

The relation between anemia and fat mass loss in different diseases was assessed in small number of studies. In cancer patients it was established that hemoglobin level positively, significantly correlated with serum albumin level. Albumin was significantly lower in patients with Hb≤10.0 g/dL compared to the levels in patients with Hb>10 g/dL. Also it was found that BMI is positively correlated with hemoglobin level [20]. Another study reported that the response to erythropoiesis-stimulating agents in patients with chronic kidney disease is influenced by body composition and fat tissue favors the body's response to given therapy [29].

In contrast to our results in healthy preadolescents the prevalence of iron deficiency and iron deficiency anemia was established significantly higher in boys and girls in the highest quartiles of percentage body fat than in peers in the lowest quartile [22].

Thus it seems substantial fat loss may be an anemia causative agent under the condition of active systemic inflammation.

Directed acyclic graph [14] for depicting potential causal structure of anemia occurrence in UC patients with taking into account undernutrition is presented in Figure 3.

CONCLUSIONS

We assume undernutrition is one of the causative factors of anemia in UC patients. Decreased serum protein level (<64 g/l) and substantial fat mass loss were associated with a high frequency of anemia. Findings in the present study could have significant implications for physicians caring for UC patients with anemia associated with undernutrition.

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