

## Anemia in patients undergoing ambulatory peritoneal dialysis: prevalence and associated factors

Anemia em pacientes submetidos à diálise peritoneal ambulatorial: prevalência e fatores associados

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### ABSTRACT

**Introduction:** Anemia is a common complication in dialysis patients, scarce studies have evaluated anemia in patients undergoing peritoneal dialysis (PD). **Objective:** This study aimed to investigate the prevalence of anemia and its associated factors in patients undergoing PD in a single center where patients have free access to agents stimulating erythropoiesis (ESA) and intravenous iron supplementation. **Methods:** Cross-sectional study analyzing the demographic, clinical and laboratory variables of 120 patients. Anemia was defined as hemoglobin (Hb) < 11 g/dl. **Results:** Patients were on PD for 17 months, and the majority of them (86%) received automated PD. The mean age was  $58 \pm 16.5$  years, and 52% were female and 29% were diabetes. Anemia was present in 34 (28%) patients. When compared with those without anemia, patients with anemia received a higher dose of iron ( $p = 0.02$ ) and had a lower concentration of triglycerides ( $p = 0.01$ ). Hb levels correlated negatively with iron ( $r = -0.20$ ;  $p = 0.03$ ) and ESA ( $r = -0.23$ ;  $p = 0.01$ ) doses and positively with albumin ( $r = 0.38$ ;  $p = 0.01$ ), triglycerides ( $r = 0.24$ ;  $p = 0.01$ ) and transferrin saturation ( $r = 0.20$ ;  $p = 0.03$ ). In multiple analyses, only the albumin concentration (beta = 0.84; 95% IC = 0.38-1.31;  $p < 0.001$ ) and ESA dose (beta = -0.06; 95% IC = 0.00-0.00;  $p = 0.02$ ) were independently associated with Hb levels. **Conclusions:** Almost 30% of PD patients had anemia, even with free access to erythropoietin and intravenous iron. The transferrin saturation and nutritional status assessed by albumin, were the factors associated with the occurrence of anemia in this population.

**Keywords:** anemia; iron; malnutrition; peritoneal dialysis.

### RESUMO

**Introdução:** A anemia é uma complicação frequente em pacientes em diálise e poucos estudos avaliaram sua ocorrência em pacientes submetidos à diálise peritoneal (DP). **Objetivo:** Este estudo teve como objetivo investigar a prevalência e fatores associados à presença de anemia em pacientes submetidos à DP de um único centro onde havia acesso irrestrito a agentes estimulantes da eritropoiese (AEE) e a suplementação de ferro intravenoso. **Métodos:** Estudo transversal que analisou variáveis demográficas, clínicas e laboratoriais de 120 pacientes. Anemia foi definida como hemoglobina (Hb) < 11g/dl. **Resultados:** Os pacientes estavam em DP por 17 meses, sendo 86% automatizada. A idade média foi de  $58 \pm 16,5$  anos, 52% dos pacientes eram do sexo feminino e 29% diabéticos. Anemia esteve presente em 34 pacientes (28%). Quando comparados com pacientes sem anemia, aqueles com anemia recebiam maior dose de ferro ( $p = 0,02$ ) e apresentavam menores triglicérides ( $p = 0,01$ ). A Hb se correlacionou negativamente com as doses de ferro ( $r = -0,20$ ;  $p = 0,03$ ) e AEE ( $r = -0,23$ ;  $p = 0,01$ ), e positivamente com albumina ( $r = 0,38$ ;  $p = 0,01$ ), triglicérides ( $r = 0,24$ ;  $p = 0,01$ ) e índice de saturação da transferrina ( $r = 0,20$ ;  $p = 0,03$ ). Na análise múltipla, a concentração de albumina (coefβ = 0,84; 95% IC = 0,38-1,31;  $p < 0,001$ ) e a dose de AEE (coefβ = -0,06; 95% IC = 0,00-0,00;  $p = 0,02$ ) foram associadas de forma independente com a Hb. **Conclusões:** No presente estudo, anemia foi observada em aproximadamente 30% dos pacientes em programa de diálise peritoneal, com uso irrestrito de AEE e suplementação intravenosa de ferro. A saturação de transferrina e o estado nutricional, avaliado pela albumina, foram os fatores independentes associados à concentração de hemoglobina nesta população.

**Palavras-chave:** anemia; desnutrição; diálise peritoneal; ferro.

## INTRODUCTION

Anemia is a common complications in patients with chronic kidney disease (CKD), and its occurrence has been associated with a worse outcomes.<sup>1</sup> If left untreated, anemia related to CKD is associated with several abnormalities, including decreased release and use of oxygen in tissues, increased cardiac output, increased heart area, ventricular hypertrophy, angina, congestive heart failure, reduce cognition and mental acuity, changes ins menstrual cycles and impaired response imunoolig.<sup>1-5</sup> In addition, anemia may slow the growth in pediatrics patients.<sup>6</sup> Data from the Brazilian Society of Nephrology (SBN) in 2013 showed that the prevalence of anemia, defined by a concentration of Hb < 11g/dl in dialysis patients was 33%, even with free access to use of eritropoetin.<sup>7</sup>

Peritoneal dialysis (PD) is currently the renal replacement therapy of choice for more than 130,000 patients worldwide, representing approximately 15% of the worldwide population on dialysis.<sup>8</sup> In Brazil, 9.2% of the patients on renal replacement therapy were on peritoneal dialysis (PD) in 2013.<sup>7</sup> Data on anemia in PD patients are scarce and controversial.<sup>9-11</sup> Core Records Indicators Study, show that, despite 85% of the PD patients receiving erythropoiesis-stimulating agents (ESA), 40% had hematocrit levels lower than 33%.<sup>9</sup> The United States Renal Data System 2013 showed that 66% of PD patients on had Hb levels lower than 11 g/dL<sup>12</sup> and national patients on PD data showed that 49% of prevalent patients on dialysis present Hb levels below 11d/dl.<sup>10</sup> Factors associated with the occurrence of anemia in this population have yet to be determined. Therefore, the aim of this study was to investigate the prevalence of anemia and its associated factors in patients undergoing PD in a single center where patients have free access to erythropoietin and intravenous iron supplementation.

## METHOD

### POPULATION

The study was a cross-sectional, retrospective design, with convenience sample, included all patients who had been in the PD in January 2010 in the Oswaldo Ramos Foundation, Federal University of São Paulo with at least three months of therapy were included, there was no exclusion criteria. In this study were analyzed 120 patients of both genders, older than 18 years.

The study was reviewed and approved by the Ethics Advisory Committee of the Federal University of São Paulo, and each patient signed the informed consent form.

## METHODS

Demographic, clinical and laboratory data were obtained from the patients' charts and included the following information: age, gender, race, education status, etiology of renal disease, previous and concomitant diseases, body mass index (BMI), residual renal function, previous predialysis treatment, length of renal replacement therapy (including time on HD, PD and renal transplant), Kt/V full and medications. The incidence of hospitalizations, infectious processes and presence of active bleeding in the last three months were recorded.

Data on the prescribed dose de ESA and iron supplementation were obtained from the patients records. According to our local protocol, all patients received iron intravenously in the dialysis unit and ESA administration was made by subcutaneously by the patients at his residence.

### LABORATORY TESTS

During the three months preceding the study, the mean values from the following laboratory tests were recorded: hemoglobin, hematocrit, ferritin, transferrin saturation (TSAT), total cholesterol and fractions, triglycerides, parathormone (PTH), albumin, potassium, ionic calcium and phosphorus.

Laboratory measurements were performed in the clinical laboratory Kidney and Hypertension Hospital. Anemia was defined as Hb < 11 g/dL.

### STATISTICAL ANALYSIS

Data were expressed as the mean and standard deviation or median and interquartile range. The patients were divided into two groups according to the presence or absence of anemia. Comparisons between groups were performed using Student's *t* test and the Mann-Whitney test when appropriate. Chi-square or Fischer tests were used for comparisons of proportions. The average Hb values were correlated with other variables using the Spearman correlation coefficient. Logistic regression analysis was performed to assess the variables associated independently with the presence of anemia and multivariate linear regression was perfomed to assess the factors

associated independently with Hb concentrations. A  $p$  value of  $< 0.05$  was considered statistically significant. All analyses were performed using SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL).

## RESULTS

The characteristics of the 120 patients in the study are shown in Table 1. Patients were predominantly middle-aged and had been on PD for 17 months, and 86% of them in automated PD. Hypertension was present in almost all patients, and diabetes in 29% of them. Iron deficiency, defined as TSAT  $< 20\%$  and/or ferritin  $< 100 \mu\text{g/L}$ , was present in 35% of the patients. Of note, 87.5% of the patients were using ESA, and 47.5% received intravenous iron supplementation.

Anemia was present in 34 patients (28.3%). Table 1 shows the comparison between patients with and without anemia. When compared to patients without anemia, those with anemia received higher doses of iron and had lower concentrations of triglycerides. There was a trend towards a higher prevalence of women in the anemic group. Notably, there was no menstrual bleeding recorded in the files. There was also a trend of lower TSAT and albumin in the anemic group. In the logistic regression analysis, no variables were independently associated with the presence of anemia when gender ( $p = 0.08$ ; 95%IC = 0.18-1.11), albumin ( $p = 0.45$ ; 95%IC = 0.23-1.92), TSAT ( $p = 0.23$ ; 95%IC = 0.95-1.01), triglycerides ( $p = 0.05$ ; 95%IC = 0.99-1.00) and iron dosage ( $p = 0.42$ ; 95%IC = 0.99-1.00) were included in the model.

Hemoglobin level correlated negatively with iron and ESA dose and positively with albumin, triglycerides and TSAT (Figure 1). There was no relation between hemoglobin and other variables (Table 2). There was a correlation between albumin and triglycerides ( $r = 0.34$ ;  $p < 0.001$ ). In multivariate analyses, only the albumin concentration and ESA dose were independently associated with Hb levels (Table 3).

## DISCUSSION

In this study, anemia was observed in 30% of patients on peritoneal dialysis with unrestricted use of ESA and intravenous iron supplementation. The transferrin saturation and nutritional status assessed by albumin, were independent factors associated with hemoglobin concentration in this population.

The prevalence of anemia in CKD patients ranges from 7% to 86%.<sup>2,13-15</sup> This large variability could be partially explained by the different criteria used to define anemia and by the heterogeneity of the studied populations, including patients on predialysis and in different renal replacement therapies. In dialysis patients, contrary to the WHO definition, anemia is characterized by Hb values below the therapeutic target.<sup>16</sup> In studies with PD patients where the anemia was defined by Hb  $< 11 \text{ g/dL}$ , prevalence ranged from 18% to 57%,<sup>11,17</sup> and when anemia was defined by Hb  $< 10 \text{ g/dL}$ , ranged from 14% to 25%.<sup>18-21</sup> A Brazilian study involving over 2,000 patients in a PD program, the presence of anemia, defined as Hb  $< 11 \text{ g/dL}$ , was found in 57% of patients starting dialysis and in 38% of patients after one year of follow-up.<sup>17</sup> In this study, the authors observed that the lack of adequate predialysis care and the presence of previous treatment in HD were the determinants factors of anemia. Notably, in this study, most of the patients had received predialysis care for a mean period of 25 months before the start DP, and one-third had received prior hemodialysis and none of these factors was associated with the presence of anemia.

The relative erythropoietin deficiency is the main cause of anemia in patients with CKD, however other factors contribute to the appearance of anemia in this population, iron deficiency is the most common.<sup>22</sup> This complication occurs in both patients with CKD in predialysis care as those undergoing dialysis, with prevalence ranging from 43%-70%.<sup>14,22,23</sup> Almost one-third of the patients had iron deficiency in the present study, and those with anemia had lower TSAT. Of note, 47% of the patients received iron supplementation; a similar rate has been described in other studies, ranging from 42%-74%.<sup>17,20</sup> However, different from the other studied populations, all patients received intravenous iron supplementation in this study.

According to the Brazilian Society of Nephrology, about 80% of dialysis patients received ESA in Brazil during 2010 and 2011.<sup>24</sup> Although 87.5% of the study population was using ESA, anemia was present in a third of these patients. The fact that ESA administration was performed subcutaneously by patients in their homes does not allow the membership check to treatment in this population and decreased adherence may have contributed to the occurrence of anemia. It should also be considered that

**TABLE 1** STUDY POPULATION CHARACTERISTICS ACCORDING TO THE PRESENCE OF ANEMIA

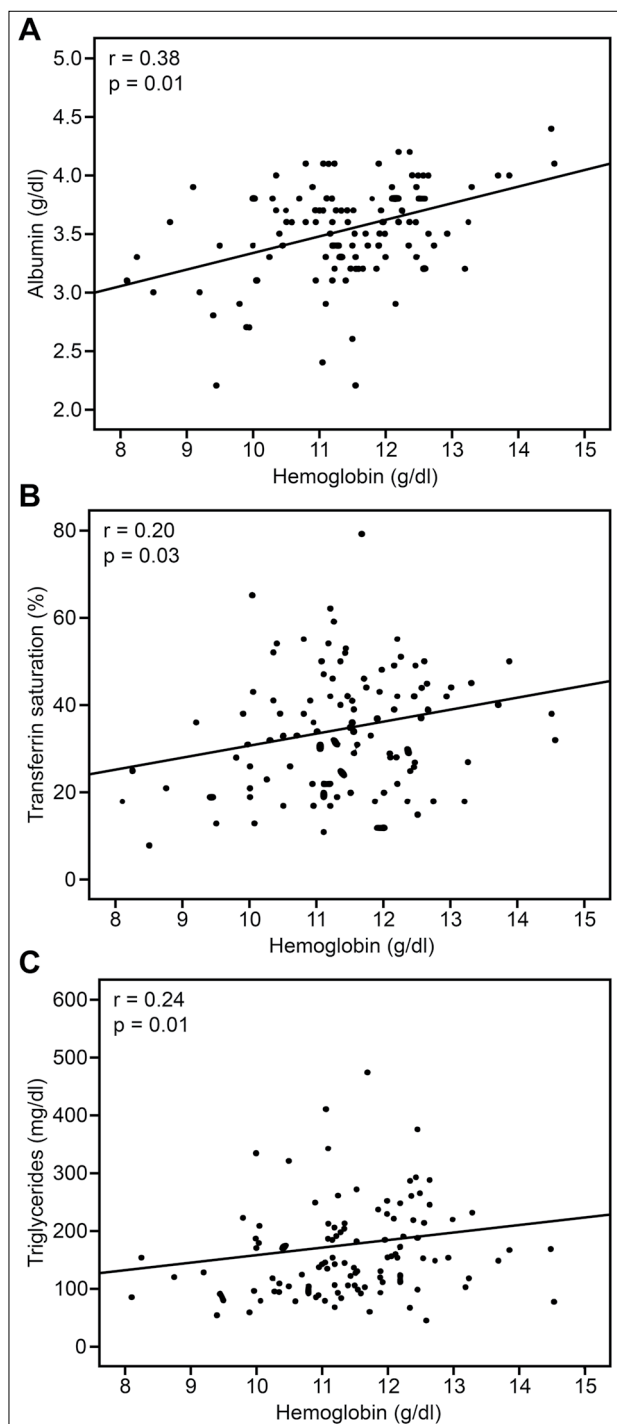
Variables	Total (n = 120)	Without anemia (n = 86)	With Anemia (n = 34)	p
Age (years)	58.1 ± 16.4	59.7 ± 14.3	56.1 ± 20	0.34
Gender female (%)	63 (52.5)	40 (47.6)	22 (64.7)	0.09
Diabetes (%)	35 (29.2)	27 (32.1)	8 (23.5)	0.35
Hypertension (%)	112 (93.3)	78 (92.9)	32 (94)	0.80
Chronic Kidney Disease Etiology				
Diabetes (%)	26 (22)	20 (24)	6 (18)	0.97
Hypertension (%)	15 (13)	11 (13)	4 (12)	
Pre dialysis therapy length (months)	12 (0-37)	11 (0-47)	7 (0-24)	0.14
Peritoneal dialysis therapy length (months)	17 (8-37)	17 (9-36)	17 (8-44)	0.98
Hospitalization previous*	5 (5)	6 (7)	1 (3)	0.67
Infection previous*	20 (17)	14 (17)	6 (18)	0.89
Bleeding previous*	0	0	0	1.0
Kt/V > 1,7 (%)	96 (80)	69 (82.1)	26 (76.5)	0.71
Residual diuresis (mL/24h)	320 (0-980)	340 (9-955)	280 (0-1060)	0.97
Characteristic membrane transport (%)				0.50
Low average I	51%	55%	41%	0.90
High average	58%	25%	37%	
Body Mass Index (Kg/m <sup>2</sup> )	25.5 ± 6.3	25.5 ± 6.5	25.7 ± 6	0.90
Weekly dose of erythropoietin (UI/week)	4000 (4000-8000)	4000 (4000-8000)	8000 (4000-11000)	0.22
Use of erythropoiesis-stimulating agents (%)	105 (87.5)	74 (88.1)	29 (85.3)	0.68
Weekly dose of iron hydroxide (mg/week)	0 (0-200)	0 (0-200)	200 (0-200)	0.02
Use of iron supplementation (%)	57 (47.5)	36 (42.9)	20 (58.8)	0.13
Hemoglobin (g/dL)	11.3 ± 1.1	11.9 ± 0.7	9.9 ± 0.7	0.01
Transferrin saturation (%)	34.8 ± 15.6	36.6 ± 16.2	30.3 ± 13.5	0.05
Ferritin (ug/L)	343 (128-631)	332 (158-646)	383 (108-708)	0.84
LDL-cholesterol (mg/dL)	98.2 ± 40	101 ± 41.6	91.5 ± 36.5	0.25
HDL-cholesterol (mg/dL)	40.1 ± 10.8	39.3 ± 10.2	42.5 ± 12.2	0.15
Triglycerides (mg/dL)	148 (103-212)	157 (121-224)	113 (89-173)	0.01
Parathormone (ng/dL)	402 (244-616)	405 (240-597)	382 (264-681)	0.82
Albumin (g/dL)	3.5 ± 0.4	3.58 ± 0.4	3.41 ± 0.4	0.06

\* Three months prior to the study.

increases and reductions in ESA doses according to the results of last months tests contribute significantly to variability in hemoglobin, which is very frequent in this population.<sup>17</sup>

The occurrence of hypoalbuminemia in about half of patients was similar to that described in populations on DP ranging from 34 to 49%.<sup>10,25</sup> Several studies have shown an association between low albumin levels and increased risk of morbidity and mortality in patients undergoing dialysis,<sup>26-30</sup> suggesting that albumin levels could indicate the presence of malnutrition and inflammation in this population.<sup>30,31</sup> Low levels of triglycerides have been linked to the presence of

malnutrition in HD patients.<sup>31</sup> In this study, we observed a correlation between triglycerides and albumin. Interestingly, we observed an association between low levels of triglycerides and the presence of anemia, which suggests that malnutrition may be an important component in the pathogenesis of anemia in this population. Moreover, a correlation between albumin concentrations and Hb was also observed, as previously described in a cohort of children on DP and patients in HD on the other hand albumin is a negative acute phase protein of inflammation and had no access to other inflammatory markers to confirm the contribution of inflammation anemia in these patients.<sup>15</sup>

**Figure 1.** Correlation between hemoglobin with albumin (A), transferrin saturation (B) and triglycerides (C).

Limitations of this study include the relatively small sample size, retrospective design, lack of other inflammatory markers and nutrition status, yet this study was able to identify factors associated with the occurrence of anemia in patients undergoing peritoneal dialysis.

**TABLE 2** CORRELATION BETWEEN HEMOGLOBIN AND OTHER VARIABLES

Variables	r	p
Age (years)	0.02	0.86
Previous predialysis treatment (months)	0.10	0.26
Length of peritoneal dialysis therapy (months)	-0.06	0.50
Length of renal replacement therapy (months)	-0.01	0.93
Body Mass Index (Kg/m <sup>2</sup> )	0.06	0.50
Weekly dose of erythropoietin (UI/week)	-0.23	0.01
Weekly dose of iron hydroxide (mg/week)	-0.20	0.03
Transferrin saturation (%)	0.20	0.03
Ferritin (ug/L)	0.12	0.20
LDL- cholesterol (mg/dL)	-0.02	0.86
HDL- cholesterol (mg/dL)	-0.12	0.20
Triglycerides (mg/dL)	0.24	0.01
Parathormone (ng/dL)	-0.03	0.76
Albumin (g/dL)	0.38	0.01

**TABLE 3** LOGISTIC REGRESSION TO DETERMINE FACTORS ASSOCIATED WITH ANEMIA

Variable	coefficient $\beta$	p	95% CI
Gender (male)	-0.26	0.20	-0.660 to 0.150
Albumin (mg/dL)	0.85	0.00	0.387 to 1.310
Transferrin saturation (%)	0.06	0.43	-0.008 to 0.019
Triglycerides (mg/dL)	0.95	0.91	-0.002 to 0.002
Weekly dose of ESA (UI/week)	-0.06	0.02	0.000 to 0.000
Weekly dose of Iron (mg/week)	-0.02	0.30	-0.003 to 0.001

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