Anemia in chronic kidney disease in a Hospital in the Northwest region to the State of Rio Grande do Sul

Authors
Cristiane Schmalz Bueno[1]
Matias Nunes Frizzo[1]

[1] Regional University of Northwestern Rio Grande do Sul (UNIJUI).

ABSTRACT

Introduction: Chronic kidney disease (CKD) has been identified in an increasing number of patients and among its consequences is the anemia. **Objective:** To verify the occurrence of anemia in patients with CKD undergoing hemodialysis at a Hospital in the South Region, Brazil, as well as their kidney profile and iron profile. **Methods:** It was performed a retrospective, descriptive and analytical study. It was analyzed 45 patient records with results from the beginning of the hemodialysis treatment until nine months later. **Results:** Over 50.0% of the patients had hypertension and diabetes and 68.8% were male. The anemia was present in 97.8% of the patients and treated with erythropoietin and/or iron. In the evaluated period occurred increase in median hemoglobin levels ($p < 0.001$), hematocrit ($p < 0.001$), ferritin, creatinine ($p < 0.001$) and urea under ($p = 0.039$). The transferrin saturation was low in 35.6% of the patients after about one year under hemodialysis treatment. There was correlation between creatinine and urea, both rising. **Conclusion:** After the introduction of treatment for anemia occurred increased plasma levels of hemoglobin and clinical improvement, even though not having a complete normalization of these levels.

Keywords: anemia; creatinine; erythropoietin; renal insufficiency, chronic; urea.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem.[1] A census carried out in Brazilian dialysis units registered with the Brazilian Society of Nephrology, reported an increasing trend in the number of dialysis patients in the last decade, and the number estimated in January 2011 was 91,314 patients. The prevalence rate of dialysis in 2011 was 475 patients/million of the population, and there are 26,680 estimated patients who will started treatment in 2011, with an incidence rate of 149 patients/million of the population, and hemodialysis was the initial treatment mode in 90.6% of the cases.[2] Progressive loss of kidney function results in clinical manifestations, of which anemia is common in CKD patients.[3-6]

The prevalence and severity of anemia are related to the kidney disease stage,[7,8] and the relative deficiency/reduction in erythropoietin (EPO) production is the main cause,[1,3] because the kidneys produce this hormone that stimulates red blood cell production and when the patient develops CKD, he/she does not

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Correspondence to:
Cristiane Schmalz Bueno.
Regional University of Northwestern Rio Grande do Sul (UNIJUI).
Rua do Comércio, nº 3000, Bairro Universitário. Ijuí, RS, Brasil.
CEP: 98700-000.
E-mail: cryssbueno@yahoo.com.br

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produce it in sufficient amounts.[9] In addition of EPO deficiency, other situations may contribute to the occurrence of anemia in CKD, such as iron, folic acid and vitamin B12 deficiency; blood loss; hemolysis, hyperparathyroidism and inflammation, and these should be investigated before the introduction of EPO replacement therapy - the most common being iron deficiency (52.0%).[7,10]

Anemia causes fatigue, reduced exercise capacity, reduced libido and cognitive function, which ultimately have a negative impact on their quality of life,[1,11] in addition to being related to heart failure, [12,13] cardiovascular diseases are the leading causes of mortality in CKD.[5] Thus, RBC indices, serum iron, transferrin and ferritin saturation, among others, are tests that may be part of the clinical investigation and monitoring of patients with CKD.[7]

In chronic kidney failure (CKF), there is also impairment in the excretion of toxic non-volatile solutes, with consequent increase in the plasma concentrations of all catabolites derived mainly from protein metabolism, characterized by increased urea and creatinine.[14] Creatinine dosage can be used as an aid in kidney function diagnosis, it is most useful and a more sensitive and specific indicator then urea;[15] however, other markers of renal function and renal damage have been investigated and may be introduced in clinical practice to assist in the diagnosis, monitoring, analysis and prognosis of kidney disease progression.[16]

Whereas anemia is one of the main consequences of CKD and, when found, requires proper treatment and monitoring, checking the tests results can characterize the hematologic changes, iron behavior dynamics, as well as urea and creatinine concentrations and their possible relations with anemia in CKF patients on hemodialysis. Thus, this study aimed at checking the occurrence of anemia in patients with CKD who underwent hemodialysis in a hospital in the northwestern region of Rio Grande do Sul, as well as the kidney and iron profiles of these patients.

Methods

Study design, sample and variables

This is a retrospective descriptive analytic study. The information was obtained from medical records of patients with CKD who were undergoing treatment in the hemodialysis ward of a hospital in the northwestern region of Rio Grande do Sul - RS, Brazil. The charts of all patients on hemodialysis were studied, and we included in the study those who had at least four routine examinations, which are quarterly held on the site. There were 105 patients on hemodialysis, of which 45 had the least number of tests required for inclusion in the study.

We studied the results from the hemoglobin, hematocrit, ferritin, serum iron, transferrin saturation, creatinine and pre-and post-hemodialysis urea tests. Anemia was defined as cases in which the hemoglobin level was < 13 g/dL for men and < 12 g/dL for women.[17] For the other tests we used adapted reference values from the Brazilian Association of Hematology and Hemotherapy[18] and the Brazilian Society of Nephrology.[19] We recorded the results from the first examination after the patients started on hemodialysis and three subsequent ones. This research project was approved by the Research Ethics Committee o Unijuí, under protocol # 143.971/2012.

Statistical analysis

The data was processed using the PASW Data Editor Statistics (version 18.0, Chicago, IL, USA) statistical package. The descriptive analysis is presented as mean ± standard deviation, relative and absolute frequency. For quantitative variables, we performed the Kolmogorov-Smirnov normality test, in which we used the parametric comparisons of independent means, we also used the Student *t* test and the nonparametric U (Mann Whitney test). In the analysis of the paired parametric variables we used the Student *t*-test; and the nonparametric Wilcoxon test for the non-parametric ones. Non-parametric variables

were expressed as median and interquartile range (IQR). In the qualitative variables, we used the Pearson chi-square test and the Fisher's Exact test. In the correlations, we used Spearman's and Pearson's tests, depending on the normality of the variables. A *p*-value < 0.05 was considered significant.

Results

The study included 45 patients with median age of 61 years, ranging between 49 and 71 years, and 2 months of time elapsed between hemodialysis treatment onset and the completion of the first test (TTTHRPE), ranging between 1-3 months; there were no statistical differences between genders. Among hemodialysis patients, 68.8% (31/45) were males and 44.0% were aged 60-79 years. Among women, 42.0% were aged 60-79 years. Table 1 shows the sample profile.

Among CKD-predisposing factors, 12 (38.7%) men had systemic hypertension (SH); three (09.8%) had *diabetes mellitus* (DM); five (16.1%) hypertension and DM; there was no information for six (19.3%) and five men had other predisposing factors (16.1%). Among women, five (35.7%) had hypertension; one (07.1%) DM; two (14.3%) hypertension and DM; there was no information for two (14.3%); and four (28.6%) had other predisposing factors.

The results of tests performed at baseline and after nine months (first and fourth tests) showed that there was a statistically significant increase in median hemoglobin levels ($p < 0.001$, $p = 0.015$ Men, Fem $p = 0.013$), hematocrit ($p < 0.001$ Men $p = 0.007$; Women $p = 0.013$), creatinine, and urea pre (creatinine $p < 0.001$ Men $p < 0.001$, $p = 0.030$ Women, urea pre: $p = 0.039$, p = Men. 0.009, $p = 0.634$ Fem), except the urea pre women (Table 2).

Among the 14 women, 13 (92.9%) had used EPO and iron at some time during treatment with hemodialysis and one (07.1%) used iron only; among men, 22 (71.0%) used EPO and iron, three (09.7%) used EPO only; one (03.2%) iron only; and for five (16.1%) we had no information on the use of these. The initially prescribed EPO doses ranged between 2000-4000 IU, also with variable dosing - according to medical criteria. Iron supplementation when in injectable form was performed using iron hydroxide saccharate III 100 mg (variable dosing according to medical criteria) and, when per os, the iron salt used was ferrous sulfate at an initial dose of 300 mg.

Table 3 shows that in the first test, hemoglobin was statistically correlated with TTTHRPE (r = 0.379 - Regular, $p = 0.01$); age (r = 0.307 - Regular, $p = 0.04$), hemoglobin in the fourth test (r -0.385 - Regular, $p < 0.001$) and hematocrit (r = -0.901 - very strong, $p < 0.001$).

The amounts of urea in the first test were correlated with age (inversely), creatinine, urea pre in the fourth test and urea post, similarly to what happened with creatinine (Table 3).

Table 1 Profile of patients under dialysis in a hospital in the northwestern portion of Rio Grande do Sul state, Brazil

	Total	Males	Females	
	Median (IIQ)	Median (IIQ)	Median (IIQ)	*p*
Age (years)	61.00 (49.00-71.00)	64.00 (53.00-71.00)	59.50 (43.00-68.00)	0.370€
TTTHRPE (months)	2.00 (1.00-3.00)	2 (1.00-3.00)	2.00 (1.00-3.00)	0.677€
Age range (years)	f (%)	f (%)	f (%)	
20-39	05 (11)	03 (10)	02 (14)	
40-59	16 (36)	11 (35)	05 (36)	
60-79	20 (44)	13 (42)	07 (50)	
≥ 80	04 (09)	04 (13)	0 (0)	
Total	45 (100)	31 (100)	14 (100)	0.641¥

IIQ: Interquartile interval (1st quartile - 3rd quartile); € Mann-Whitney U test; ¥ Fischer's Exact Test; M ± SD: Mean ± standard deviation; TTTHRPE: Time elapsed between hemodialysis treatment onset and the first test (months); f (%): Absolute and relative frequency.

Table 2 Comparison of sequential tests, after starting hemodialysis, in patients from a hospital in the northwestern portion of Rio Grande do Sul state, Brazil

	Total	Males	Females	
	Median (IIQ)	Median (IIQ)	Median (IIQ)	*p*
Hemoglobin				
1st test	8.00 (7.40-9.40)	8.10 (7.60-9.50)	7.55 (6.92-8.75)	0.162€
2nd test	8.30 (7.25-9.30)	8.30 (7.10-9.50)	8.20 (7.45-8.85)	0.912€
3rd test	8.90 (7.75-10.45)	8.80 (7.70-10.40)	9.15 (7.82-11.65)	0.382£
4th test	8.90 (7.65-10.95)	8.40 (7.40-11.50)	9.20 (8.37-10.37)	0.412€
$p^{2¥}$	< 0.001*	0.015*	0.013*	
Hematocrit				
1st test	24.60 (22.40-28.85)	25.00 (22.90-29.90)	24.00 (21.57-26.62)	0.281€
2nd test	25.80 (21.85-29.10)	25.90 (21.60-29.20)	25.60 (22.30-28.32)	0.893€
3rd test	27.40 (22.75-32.55)	27.10 (22.50-32.10)	28.40 (23.82-35.85)	0.525£
4th test	28.60 (23.05-33.35)	27.80 (22.40-34.30)	28.65 (26.07-31.17)	0.704€
$p^{2¥}$	< 0.001*	0.007*	0.013*	
Ferritin				
1st test	323.00 (175.50-725.00)	364.00 (242.00-727.00)	158.50 (59.75-624.75)	0.044€*
2nd test	343.00 (108.00-701.00)	343.00 (108.00-701.00)	175.00 (58.30-613.25)	0.106€
3rd test	376.00 (119.00-727.00)	391.00 (141.00-690.00)	226.00 (65.40-894.12)	0.492€
4th test	575.00 (176.00-917.50)	576.00 (242.00-880.00)	372.00 (150.25-1149.00)	0.932€
$p^{2¥}$	0.212	0.481	0.198	
Iron				
1st test	64.00 (56.00-91.30)	69.00 (46.10-91.60)	51.35 (40.50-78.50)	0.234€
2nd test	64.30 (39.85-76.00)	64.30 (39.00-84.00)	62.30 (38.95-72.70)	0.447€
3rd test	62.20 (42.95-81.75)	62.20 (48.00-81.40)	59.80 (36.00-94.10)	0.778£
4th test	64.60 (41.35-83.95)	64.60 (43.70-84.00)	63.60 (39.00-83.92)	0.990€
$p^{2¥}$	0.584	0.347	0.594	
Transferrin saturation				
1st test	26.06 (17.55-37.45)	30.00 (19.76-39.00)	20.06 (13.67-33.73)	0.207€
2nd test	25.00 (14.49-33.25)	25.00 (15.09-36.00)	24.15 (11.23-30.04)	0.447€
3rd test	24.00 (16.50-37.00)	25.00 (19.59-34.19)	23.00 (13.32-47.93)	0.816€
4th test	27.20 (16.50-37.45)	27.00 (16.00-37.90)	29.52 (16.26-36.43)	0.941€
$p^{2¥}$	0.910	0.688	0.331	
Creatinine				
1st test	7.00 (5.29-9.18)	6.81 (5.15-8.74)	8.11 (6.07-9.92)	0.207£
2nd test	8.59 (5.96-9.88)	8.71 (5.79-9.85)	8.47 (6.73-10.24)	0.447£
3rd test	8.60 (7.38-10.64)	9.10 (6.52-10.66)	8.39 (7.62-10.64)	0.816£
4th test	9.52 (7.22-10.95)	9.86 (6.798-11.40)	9.18 (7.75-9.77)	0.941£
$p^{2£}$	< 0.001*	< 0.001*	0.030*	
Urea Pre				
1st test	152.00 (124.50-181.50)	152.00 (113.00-185.00)	154.00 (127.50-177.75)	0.733£
2nd test	145.00 (125.50-192.50)	157.00 (124.00-198.00)	138.50 (130.75-180.25)	0.922€
3rd test	166.00 (128.00-193.50)	171.00 (128.00-194.00)	157.00 (136.50-196.50)	0.908£
4th test	171.00 (139.00-204.00)	181.00 (142.00-204.00)	145.00 (124.25-190.75)	0.064£
$p^{2£}$	0.039*	0.009*	0.634	
Urea Post				
1st test	63.00 (51.00-80.00)	63.00 (51.00-81.00)	63.00 (50.75-75.75)	0.941€
2nd test	62.00 (49.50-77.00)	66.00 (50.00-80.00)	55.50 (45.00-66.25)	0.088€

Continued Table 2.

3rd test	60.00 (52.00-83.00)	67.00 (54.00-89.00)	56.50 (45.50-62.25)	0.044€*
4th test	70.00 (55.00-83.50)	74.00 (62.00-88.00)	59.00 (42.25-73.75)	0.006£*
p^{2}¥	0.378	0.095	0.315	

IIQ: Interquartile interval (1st quartile - 3rd quartile); M ± SD: Mean ± standard deviation; € Mann-Whitney U test; £ Student *t*-test; ¥ Wilcoxon test; p^2 comparison of the mean between the first and fourth tests; * $p < 0.05$, statistically significant.

Table 3 Correlation between hemodialysis patient variables from a hospital in the northwestern portion of Rio Grande do Sul state, Brazil

	Hemoglobin in the 1st test	
	r	*p*
TTTHRPE	0.379	0.01*
Age	0.307	0.04*
Hemoglobin in the 4th test	-0.385	< 0.001*
Hematocrit	-0.901	< 0.001*
Ferritin	0.066	0.67
Iron	0.254	0.93
Transferrin saturation	0.153	0.33
Creatinine	-0.159	0.30
Urea Pre	0.069	0.65
Urea Post	0.181	0.23
	Urea Pre in the 1st test	
	r	*p*
TTTHRPE	0.041	0.80
Age	-0.303	0.04*
Hemoglobin	0.054	0.72
Hematocrit	0.022	0.88
Ferritin	0.104	0.50
Iron	0.117	0.44
Transferrin saturation	0.204	0.18
Creatinine	0.478	< 0.001*
Urea Pre in the 4th test	0.331	0.02*
Urea Post	0.609	< 0.001*
	Creatinine in the 1st test	
	r	*p*
TTTHRPE	0.151	0.32
Age	-0.443	0.02*
Hemoglobin	-0.159	0.30
Hematocrit	-0.213	0.16
Ferritin	0.026	0.86
Iron	-0.065	0.67
Transferrin saturation	0.410	0.80
Creatinine in the 4th test	0.579	< 0.001*
Urea Pre	0.478	< 0.001*
Urea Post	0.361	0.01*

TTTHRPE: Time elapsed between hemodialysis treatment onset and the first test; * $p < 0.05$, statistically significant.

In the correlation analysis between patients with hemoglobin concentration below normal (in the first and fourth tests) and patients with low, normal and high transferrin saturation (the first and fourth tests); low, normal and high iron; high creatinine and low normal and high ferritin; there was a significant linear correlation between low hemoglobin and normal ferritin in the first test (r = 0.397 - Regular, $p = 0.054$).

Anemia was present in 44 patients (97.8%) in the first test after the start of hemodialysis and after nine months of treatment, 41 (91.1%) had the same. On Table 4, we see hemoglobin variations stratified by gender.

Table 5 shows the distribution of patients according to the results of the hematological, iron and kidney tests.

Discussion

A slightly higher percentage of patients on hemodialysis were male (68.8%), as observed in the study by Sesso *et al.*[20] and Ammirati *et al.*,[21] who reported 57.0% and 56.6%, respectively. It is possible that the higher number of men is due to the fact that, generally, women are more concerned about health care, following more strictly the treatment of hypertension and DM; which prevents or prolongs the time to effect the consequences, CKF among them. Gutierrez *et al.*[22] reported that the action of men in taking care of themselves often occurs indirectly, happening on a chain of relationship and influences where professionals teach the women, and they teach their male companions, and we can say that women are still considered as the basis for health care.

Hypertensive and diabetics, and patients with a family history of CKD are more likely to develop CKD,[23] and this study shows that more than half of the patients had predisposing

Table 4 Hemoglobin variables comparison in the first and fourth test, classified by gender, from patients of a hospital in the northwestern portion of Rio Grande do Sul state, Brazil

	Total	Males	Females
Hemoglobin (first test)*	f (%)	f (%)	f (%)
A	05 (11.5)	04 (12.9)	01 (07.7)
B	24 (54.5)	16 (51.6)	08 (61.5)
C	13 (29.5)	09 (29.1)	04 (30.8)
D	02 (04.5)	02 (06.4)	0 (0)
Hemoglobin (fourth test)*			
A	05 (12.2)	05 (17.2)	0 (0)
B	12 (29.3)	11 (37.9)	01 (08.3)
C	14 (34.1)	06 (20.7)	08 (66.7)
D	10 (24.4)	07 (24.1)	03 (25.0)
Hemoglobin (first test) below 11 g/dL	42 (93.3)	29 (93.5)	13 (92.9)
Hemoglobin (fourth test) below 11 g/dL	34 (75.6)	22 (70.9)	12 (85.7)
Hemoglobin (first test) between 11 and 12 g/dL	02 (04.4)	02 (06.5)	0 (0)
Hemoglobin (fourth test) between 11 and 12 g/dL	06 (13.3)	06 (19.4)	0 (0)

* Classification according to gender. For women - A: 4.0 to 5.9 g/dL; B: 6.0 to 7.9 g/dL; C: 8.0 to 9.9 g/dL; D: 10.0 to 11.9 g/dL. For men: A: 5.0 to 6.9 g/dL; B: 7.0 to 8.9 g/dL; C: 9.0 to 10.9 g/dL; D: 11.0 to 12.9 g/dL.

Table 5 Comparison of hematological variables, kidney and iron laboratorial profiles from the first and fourth tests of hemodialysis patients from a hospital in the northwestern portion of Rio Grande do Sul state, Brazil

	Total	M	F	
First test	f (%)	f (%)	f (%)	*p*
Hemoglobin				0.809¥
< 13 g/dL for men and < 12 g/dL for women	44 (97.8)	31 (100)	13 (92.9)	
≥ 13 g/dL for men and ≥ 12 g/dL for women	01 (2.2)	0 (0)	01 (7.1)	
Hematocrit				0.530¥
< 39% for men and < 35% for women	43 (95.6)	30 (96.7)	13 (92.9)	
Between 39 and 53% for men and 35 and 47% for women	02 (4.4)	01 (3.3)	01 (7.1)	
Ferritin				0.322β
Between 22.0 and 322.0 ng/ml for men and 10.0 and 291.0 ng/ml for women	24 (53.3)	15 (48.4)	09 (64.3)	
> 322.0 ng/ml for men and > 291.0 for women	21 (46.7)	16 (51.6)	05 (35.7)	
Iron				0.411¥
< 35 mcg/dL	06 (13.3)	04 (12.9)	02 (14.3)	
Between 35 and 150 mcg/ml	34 (75.6)	22 (71.0)	12 (85.7)	
> 150 mcg/dL	05 (11.1)	05 (16.1)	0 (0)	
Transferrin saturation				0.184β
< 20%	15 (33.3)	08 (25.8)	07 (50.0)	
Between 20 and 55%	27 (60.0)	20 (64.5)	07 (50.0)	
> 55%	03 (6.6)	03 (9.7)	0 (0)	
Creatinine				-
Between 0.6 and 1.3 mg/dL	0 (0)	0 (0)	0 (0)	
> 1.3 mg/dL	45 (100)	31 (100)	14 (100)	
Urea Pre				-
Between 10 and 45 mg/dL	0 (0)	0 (0)	0 (0)	
> 45 mg/dL	45 (100)	31 (100)	14 (100)	
Urea post				0.874¥
Between 10 and 45 mg/dL	07 (15.5)	05 (16.1)	02 (14.3)	
> 45 mg/dL	38 (84.5)	26 (83.9)	12 (85.7)	

Continued Table 5.

Fourth test				
Hemoglobin				0.393β
< 13 g/dL for men and < 12 g/dL for women	41 (91.1)	29 (93.5)	12 (85.7)	
≥ 13 g/dL for men and ≥ 12 g/dL for women	04 (8.9)	02 (6.5)	02 (14.3)	
Hematocrit				0.649β
< 39% for men and < 35% for women	40 (88.9)	28 (90.3)	12 (85.7)	
Between 39 and 53% for men and 35 to 47% for women	05 (11.1)	03 (9.7)	02 (14.3)	
Ferritin				0.217¥
< 322.0 ng/ml for men and < 291.0 for women	01 (2.2)	0 (0)	01 (7.1)	
Between 22.0 and 322.0 ng/ml for men and between 10.0 and 291.0 ng/ml for women	16 (35.6)	10 (32.3)	06 (42.9)	
> 322.0 ng/ml for men and > 291.0 for women	28 (62.2)	21 (67.7)	07 (50.0)	
Iron				0.522¥
< 35 mcg/dL	05 (11.1)	04 (12.9)	01 (7.1)	
Between 35 and 150 mcg/ml	39 (86.7)	27 (87.1)	12 (85.7)	
> 150 mcg/dL	01 (2.2)	0 (0)	01 (7.1)	
Transferrin saturation				0.184β
< 20%	16 (35.6)	11 (35.5)	05 (35.7)	
Between 20 and 55%	24 (53.3)	16 (51.6)	08 (57.1)	
> 55%	05 (11.1)	04 (12.9)	01 (07.1)	
Creatinine				-
Between 0.6 and 1.3 mg/dL	0 (0)	0 (0)	0 (0)	
> 1.3 mg/dL	45 (100)	31 (100)	14 (100)	
Urea Pre				-
Between10 and 45 mg/dL	0 (0)	0 (0)	0 (0)	
> 45 mg/dL	45 (100)	31 (100)	14 (100)	
Urea Post				0.139β
Between 10 and 45 mg/dL	05 (11.1)	02 (6.5)	03 (21.4)	
> 45 mg/dL	40 (88.9)	29 (93.5)	11 (78.6)	

M: Males; F: Females; f (%): Absolute and relative frequencies; ¥ Fischer's Exact Test; β Pearson's Chi-Square Test.

factors such as hypertension, *diabetes mellitus*, or both. In the study led by Ammirati *et al.*[21] Most of the patients had arterial hypertension and *diabetes mellitus*. Thus, we highlight the importance of controlling these factors, to delay and/or prevent its progression to CKF and its consequences, whereas patients with the aforementioned chronic diseases are in the risk group, which ultimately facilitate kidney injury.[23]

Most had anemia shortly after the start of hemodialysis (97.8%), which reinforces that this is common in patients with CKD. In a study held in Iran, Afshar *et al.*[24] found that, among patients with CKD who underwent hemodialysis, 85.0% had anemia, which is the same percentage found in another study involving patients from a kidney clinic in Santa Catarina.[25] In the study led by Pedruzi *et al.*,[26] 62.0% of hemodialysis patients had anemia, but these were on hemodialysis for more than 6 months. The higher percentage found in our study is probably due to the fact that this has been described for the first examination after initiation of treatment with hemodialysis.

In any event, after a period of approximately 12 months on hemodialysis, 91.1% of patients still had anemia. The significant increase in median hemoglobin concentration ($p < 0.001$) over time on hemodialysis (Table 2), as well as the increased number of patients in the groups with a higher concentration of stratified hemoglobin (Table 4), shows a reduction in anemia severity, even if this had still remained, and it is related to the introduction of EPO and/or iron use during hemodialysis, as well as increasing hematocrit. It is noteworthy

that in our study, when patients began hemodialysis they were mostly with anemia but without treatment (EPO and/or iron). When starting EPO and/or iron replacement, there is an expected increase in hemoglobin concentration and hematocrit.

The administration of EPO improves clinical outcome and the patient's quality of life is essential in controlling anemia.[27] Before its use, it is necessary to ensure that the patient has adequate iron stock to achieve and maintain planned hemoglobin levels. Iron supplementation maximizes hemoglobin levels, since this metal is essential for the treatment of anemia[27,28] and its reduction in CKD patients caused by chronic blood loss, and the possible functional deficiency of the metal can lead to iron-deficiency anemia.[5] Clinical improvement is due to EPO; iron supplementation is closely related to the loss also by hemodialysis, but helps reduce anemia.

According to Bregman & Pecoits-Filho,[29] the ideal hemoglobin range in CKD patients should be between 11 to 12 g/dL, and shall not be less than 11 g/dL, and higher values are not associated with better survival, there is even greater tendency for mortality. On first examination, 95.6% of patients had hemoglobin levels below 11 g/dL, dropping to 77.8% of patients having this level in the fourth test. There was an increase in the number of patients with hemoglobin levels between 11 and 12 g dL from the first (4.4%) to the fourth examination (13.3%); however, no woman maintained hemoglobin levels within this range - considered adequate (Table 4). Ammirati *et al.*[21] found that maintaining hemoglobin levels within a target range is difficult, since most of the patients in their study had high amplitude fluctuations. For these authors, the proportion of patients with hemoglobin within the target in each month during the study period ranged from 42.0% to 61.0%, averaging 50.0%, values that were higher than those found in our study.

The positive correlation between low hemoglobin and normal ferritin (the first test) allows us to report that anemia in CKD occurs, initially and overall, with normal ferritin levels. It is noteworthy that, generally, in chronic disease anemia serum ferritin is normal or high,[30] as it was observed in the present study. CKD is considered an inflammatory condition that leads to elevated serum levels of several inflammation markers,[10] ferritin among them, even in the lack of iron.[31] In the first test (Table 5), ferritin was normal (53,3%) or high (46.7%), and in the fourth test, 2.2% had low ferritin, 35.6% normal and 62.2% had high ferritin; these results can be expected in an inflammatory situation. Only one patient showed a decrease in serum ferritin between the first and the fourth tests, probably by secondary iron deficiency, since this patient had transferrin saturation (fourth test) below 20.0%.

Due to elevated ferritin by inflammation, transferrin is saturated, since it functionally evaluates iron available for erythropoiesis, and in patients with more advanced CKD stages, transferrin saturation index below 20.0% has a sensitivity of about 80.0% in identifying cases of absolute iron deficiency anemia.[32,33] Some patients had elevation of serum iron and transferrin saturation values above the reference, probably due to treatment with oral iron and/or injectable and/or with EPO, which may have resulted in a metal overload for these patients.

In 33.3% of patients, transferrin saturation was below 20% in the first test, rising to 35.6% in the fourth test. Possibly, these were patients with secondary iron deficiency, since iron depletion is a complication of hemodialysis, due to the process itself and the repeated phlebotomies carried out for the tests, with a loss of about 100 mg iron/month.[31]

In addition, this iron deficiency may have been due to increased hepcidin because of inflammatory mediators acting on the liver, stimulating its production.[31] This peptide blocks the duodenal absorption of iron, providing a situation of absolute iron deficiency, characterized by absence of iron in the patient's deposits (high serum ferritin levels and reduced transferrin saturation). Hepcidin is also active in the reticuloendothelial system, preventing the mobilization of iron deposits contained

in macrophages, causing a state of functional iron deficiency, characterized by no utilization of the iron present in the deposits (high serum ferritin and low transferrin saturation).[5,10] In a multicenter cross-sectional study involving patients with CKD in pre-dialysis stage from the states of SP, RJ, MG and PR, the authors[3] found transferrin saturation below 20% in 21.0% of patients and ferritin < 100 ng/ml in 53.0%; thus, it can be assumed that iron deficiency occurs in some patients during progressive loss of renal function, but related to increased hepcidin due to the inflammatory response, which could explain the low iron concentration in the first test after hemodialysis onset in our study.

Regarding kidney function, there was a significant increase in median concentrations of creatinine and urea pre within the study period (Table 2). On the first test, creatinine and urea were elevated (100.0% in both), and only a few patients reached urea values considered normal after hemodialysis (15.5%), which also occurred in general in the fourth test (Table 5). In the study led by Draczevski & Teixeira,[25] 50.0% of patients reached values of urea post within the reference range. Despite the difference with our study, urea values of all patients were reduced, even if they did not reach reference values, and demonstrate that hemodialysis fulfilled its function, but without statistical significance.

Creatinine values remained above those considered normal reference in all tests. The increase of two kidney markers from the first to the fourth tests, assessed by two markers, reflects the buildup of normally removed substances in part by glomerular filtration, which could be related to kidney damage. However, these markers suffer interference from many factors and may be also increased, among others, due to higher protein intake (urea) and increased muscle mass (creatinine).[16] Since malnutrition is a marker of poor prognosis in CKD patients, and the low calorie-protein intake is a major cause of malnutrition,[34] the raise in urea concentration may be considered a positive factor, since it may reflect an improvement in caloric and protein intake. Creatinine increase may reflect an improvement in nutritional status, such as increased muscle mass, and in a study, serum creatinine correlated positively with mental component subscale in assessing the quality of life of patients who underwent hemodialysis, which also describes that the creatinine level may be associated with better quality of life.[35]

Serum creatinine is used as an index of renal function, but it is not a very sensitive method, because its concentration is affected by factors other than glomerular filtration, such as individuals with reduced muscle mass, after excessive intake of cooked meat, malnutrition and certain medications that can interfere with tubular secretion of creatinine or the laboratory technique.[34] Still, creatinine is used as a non-isolated marker and one of the ways to monitor kidney function development is to follow through on its serum dosage. With respect to urea, it is not exclusively excreted by the kidneys, and it is considered a weak predictor of glomerular filtration, since a high percentage of it returns to the same plasma by passive diffusion, in addition to diet and the rate of hepatic production interfering and altering plasma values. It is used in joint determination with serum creatinine.[16]

As one can see, there was a joint increase of serum creatinine and urea concentrations, because there was a correlation between creatinine and urea (pre and post), and creatinine between the first and the fourth tests; urea in the first and fourth tests and urea post in the first and fourth tests (Table 3), showing a progressive increase from the first to the fourth tests.

The main cause of anemia in CKD patients is a deficiency in EPO production by injury to kidney peritubular cells and its prevalence increases with decreased in kidney function.[5,31] Accordingly, kidney injury is linked to anemia, but there was no correlation between low hemoglobin

concentration and high concentrations of urea or creatinine (Table 3).

The results of this study have limitations such as the small number of patients, the relatively short follow-up period, the reference ranges considered, as well as the methods used to obtain the results, which were not investigated. In addition, kidney function was evaluated from urea and creatinine results, even with new markers being introduced, but which are not part of routine laboratorial practice.

Conclusions

By analyzing some hematological and biochemical parameters, we found that most patients on hemodialysis developed anemia due to CKF; however, after starting anemia treatment, there were increased concentrations of hemoglobin, reducing its severity, although few patients reached levels considered adequate.

As a consequence of hemodialysis and CKD - having inflammatory characteristics, there was a reduction in the concentrations of iron and/or in the functional impairment of such metal and increasing concentration of kidney markers, which may reflect increased protein intake and better nutritional status, with possible muscle mass increase; but there was no relationship between this increase and anemia. Anemia treatment with EPO is required. As iron deficiency may be present, iron supplementation is essential when needed, since replacement of EPO alone is not enough when there is inadequate iron supply.

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