The frequency of anemia and main etiologies in patients with recently diagnosed chronic kidney disease without dialysis

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Abstract

Introduction: the prevalence of anemia in patients with non-dialysis chronic kidney disease (NDCKD) affects a large percentage of the population and is higher at lower glomerular filtration rates (GFRs). Various factors are involved in its etiology.

Objective: to evaluate the frequency of anemia in patients with NDCKD in a nephroprotection program throughout their different stages and main etiologies, and analyze the overall iron deficiency in this group of patients, regardless of whether they had anemia.

Materials and method: patients referred to the nephrology service due to impaired kidney function or a lower-than-expected GFR for their age, seen between January 2018 and January 2022 in the nephrology department at Hospital de Caldas-Universidad de Caldas, and who met the criteria for chronic kidney disease. They all underwent testing which showed if they had anemia, its most likely origin and their iron deficiency regardless of their GFR.

Results: one thousand three hundred twenty-nine patients were evaluated, with 725 ultimately included. Sixty-seven percent were in Stage 3 CKD, with an average age of approximately 64 years. Regardless of their anemia status, an absolute iron deficiency was found in 10.7%, a functional deficiency in 5.8%, folic acid deficiency in 0.6%, and vitamin B12 deficiency in 13.5% of the patients. Hemoglobin progressively decreased beginning at Stage 2, reaching an average level of 11.5 to 9.6 in Stages 4 and 5, respectively. Hyperparathyroidism was found in 36.3% of the patients, with vitamin D levels falling significantly as the GFR decreased. Anemia was found in 18.62% of the patients, with Stage 4 and 5 patients affected more often (41.25 - 85%, respectively). In this group, 23.0% had an absolute iron deficiency and 9.6% a functional deficiency. Only 0.74% had folic acid deficiency, and 11.9% had vitamin B12 deficiency. Altogether, 56.30% of anemic patients had PTH values compatible with hyperparathyroidism, with lower vitamin D levels at lower GFRs.

Conclusions: anemia affects a significant proportion of patients with NDCKD and is more frequent at lower GFRs. Its etiology varies, with notable iron deficiency, vitamin B12 deficiency and secondary hyperparathyroidism. **(Acta Med Colomb 2023; 48. DOI: https://doi.org/10.36104/amc.2023.2861).**

Keywords: *chronic kidney disease, anemia, iron, hyperparathyroidism.*

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Introduction

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, chronic kidney disease (CKD) is defined by the presence of kidney damage lasting for more than three months (1). In the group of patients without dialysis, anemia is considered to exist in adults and children over the age of 15 if the hemoglobin is less than 13 g/dL in males and less than 12 g/dL in females (2). Its prevalence increases as GFR decreases, affecting between 50.5 and 53.4% of patients with stage 4 and 5 CKD, respectively (3). It has a multifactorial origin, with people generally thinking that it is usually caused by a lack of erythropoietin, but other factors are involved, such as absolute or relative (functional) iron reduction, a shortened erythrocyte half-life, vitamin deficiencies (folic acid, vitamin B12) and uncontrolled hyperparathyroidism (4-7).

The presence of anemia in patients with non-dialysis CKD (NDCKD) can lead to a series of complications, including accelerated kidney deterioration (8,9), impaired quality of life (10), more hospital admissions with longer stays (11) and lower long-term survival (12-14).

This study evaluated the frequency of anemia in patients with NDCKD throughout its different stages and main etiologies. Overall iron deficiency in the group of patients

with NDCKD was also analyzed, regardless of whether they had anemia, in light of recent evidence of the importance of treating iron deficiency in special groups like patients with heart failure and reduced ejection fraction (15).

Materials and method

All patients with a nephrology consult due to impaired kidney function or a lower-than-expected glomerular filtration rate (GFR) for age seen from January 2018 to January 2022 in the nephrology department at Hospital de Caldas-Universidad de Caldas were included. Of these, stage 1-5 CKD patients (according to the GFR calculated using the Modification of Diet in Renal Disease [MDRD] formula) were selected based on imaging results, the kidney biopsy report or the presence of other criteria according to the KDIGO guidelines (1). This group of patients was then included in a nephroprotection program with the goal of slowing kidney damage progression.

The following tests (focusing on blood tests) were ordered for all these patients as part of the program, regardless of their GFR: a complete blood count (including hemoglobin, MCV, MCHC, RDW, WBC and platelets), serum iron, ferritin, % transferrin saturation, folic acid, vitamin B12, and PTH.

The patients were considered to be anemic when the hemoglobin was less than 13 g/dL in males and less than 12 g/dL in females. Folic acid deficiency was defined as serum levels less than 3 ng/mL, with vitamin B12 deficiency being less than 300 pg/mL, and hyperparathyroidism being PTH levels greater than 65 pg/mL.

Absolute iron deficiency was defined as ferritin less than 30 ng/mL, regardless of the percent transferrin saturation, and functional iron deficiency was ferritin greater than 100 ng/mL with a transferrin saturation of less than 20%.

Results

A total of 1,329 patients were evaluated; 604 did not meet the CKD criteria or did not undergo all the tests ordered, and 725 patients were ultimately enrolled. When classified according to their MDRD-calculated GFR they were distributed as shown in Table 1, with stage 3 having the most patients and with an average age of 64 years.

Overall, and regardless of whether they had anemia, the 725 patients had the following deficiencies: absolute iron: 78 (10.7%), functional: 42 (5.8%), folic acid: 4 (0.6%), and vitamin B12: 98 (13.5%). Hemoglobin decreased progressively after stage 2, reaching an average value of 11.5-9.6 for stages 4 and 5, respectively, although only three patients were enrolled in stage 1 (Figure 1).

Parathyroid hormone levels compatible with hyperparathyroidism were found in 263 patients (36.3%), with progressive PTH elevation as the GFR decreased, along with a significant fall in vitamin D levels (Figures 2 and 3).

Anemia was detected in 135 patients (18.62%), more often affecting patients in stages 4 and 5, with percentages between 41.25 and 85%, respectively (Table 1).

The following deficiencies were found in this group of patients with anemia: absolute iron in 31 (23.0%), and functional in 13 (9.6%). The absolute and functional deficits mainly affected patients in stage 3, concentrating 67.8 and 61.5% of the total, respectively. Only one patient had a folic acid deficiency (0.74%).

Sixteen patients had vitamin B12 deficiency (11.9%), mainly in stages 3 and 4.

Parathyroid hormone values compatible with hyperparathyroidism in anemic patients were found in 76 patients (56.30%). In this group of anemic patients, vitamin D had a mean of 27.25 (SD: 10.87). As with the total patients, the lower the GFR, the higher the PTH and the lower the vitamin D level.

Table 1. *Patient characteristics according to CKD stage. C*

Characteristic	CKD					P*
	1 n=3	2 n=142	3 n=486	4 n=80	5 n=14	
Age, median - IQR	18 (18-22)	54 (17 – 66.5)	64 (27 – 73)	64.5 (30 – 75)	63 (40 – 67.5)	NA
Sex, n - % Female Male	 3 (0.75%) 0 (0.0%)	 80 (18.6%) 62 (21.0%)	 289 (67.2%) 197 (66.8%)	 48 (11.2%) 32 (10.9%)	 10 (2.3%) 4 (1.4%)	NA
Anemia, n - % NO YES	 2 (0.34%) 1 (0.74%)	 133 (22.5%) 9 (6.7%)	 406 (68.8%) 80 (59.3%)	 47 (8.0%) 33 (24.4%)	 2 (0.34%) 12 (8.9%)	
Hemoglobin, median - IQR	12 (11.2 – 15.3)	13.4 (11.2 – 14.5)	12.8 (9.1 – 13.9)	11.5 (9.4 – 12.7)	9.6 (8.1 – 11.2)	0.000
Serum iron, median - IQR	31.6 (31.6 – 81.2)	69.2 (19.8 – 92.3)	65.3 (12.7 – 84.5)	54 (25.1 – 70.0)	55.0 (22.0 – 64.7)	0.000
Ferritin, median – IQR	5.1 (5.1 – 28.2)	62.0 (6.7 – 109.0)	57.4 (3.5 – 105.4)	75.5 (9.3 – 129.0)	67.0 (32.4 – 187.5)	0.031
% transferrin sat, median – IQR	6.6 (6.6 – 23.6)	23.4 (6.0 – 29.6)	21.3 (4.2 – 27.4)	20.2 (7.4 – 24.7)	21.2 (12.8 – 25.7)	0.01
PTH median – IQR	36.1 (13.5 – 39.5)	49.3 (34.7 – 62.0)	54.1 (41.7 – 74.9)	97.4 (63.3 –145.0)	222.0 (159.0 – 278.0)	0.01
Vitamin D median – IQR	31.0 (18.9 – 31.6)	26.9 (22.0 – 34.9)	26.3 (20.7 – 32.7)	25.3 (19.1 – 31.4)	13.1 (10.4 – 16.5)	0.02

IQR: interquartile range. *Wilcoxon.

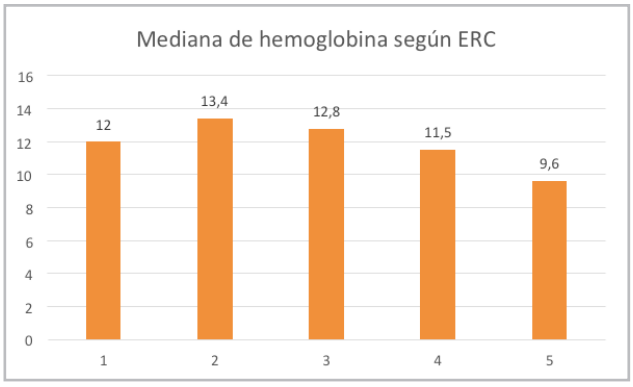

Figure 1. *Median hemoglobin in all the patients with CKD.*

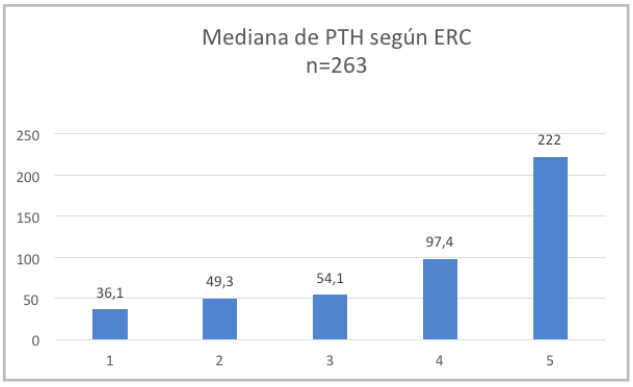

Figure 2. *PTH level according to the CKD stage.*

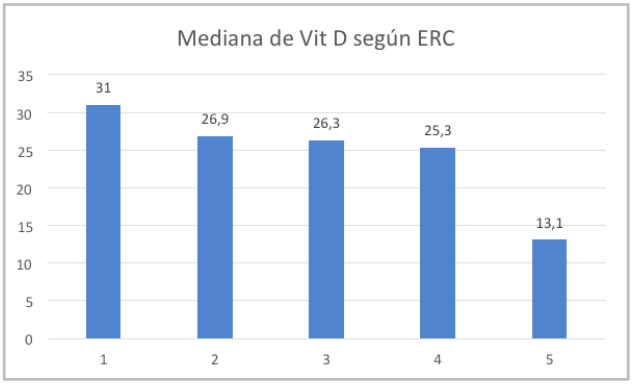

Figure 3. *Vitamin D levels according to CKD stage.*

Discussion

Anemia in patients with NDCKD leads to various complications, which can be avoided with appropriate treatment. The most important challenge for physicians caring for this group of patients is to determine the etiology of the anemia. In these patients, a global iron deficiency has been found in 40% of women and 21% of men, but the incidence may reach 59-69%, respectively, when the GFR is less than 20 mL/min (16, 17). Iron deficiency may be absolute when the amount of iron in the liver, spleen and bone marrow is low; or functional when there is adequate iron storage in the body, but it cannot be delivered for erythropoiesis.

The main causes of absolute iron deficiency in NDCKD are excessive blood loss (mainly gastrointestinal), inadequate iron intake (deficient diet), and inadequate iron absorption. High hepcidin levels, which are common in CKD, contribute to the latter (18). A functional deficiency occurs in CKD because it causes a state of chronic inflammation which stimulates hepatic hepcidin synthesis, leading to ferroportin internalization and an inability to export iron from the storage cells (enterocytes, macrophages) (19).

The KDIGO guidelines for managing anemia in patients with NDCKD suggest limiting iron storage evaluation and monitoring to patients with anemia for whom treatment with erythropoiesis-stimulating agents is being considered (2). This can leave a large group of patients with a need for iron but without anemia, who may require treatment, a relevant aspect in light of recent evidence of the cardiovascular benefits of parenteral iron therapy in patients with heart failure (20, 21).

Overall, our study found an absolute iron deficiency in 10.7% of the patients and a functional deficiency in 5.8%. Folic acid deficiency was only found in 0.6%, and vitamin B12 deficiency in 13.5%. Parathyroid hormone levels compatible with hyperparathyroidism were found in 36.3%, which suggests that these variables should be routinely measured in all patients with CKD, regardless of their stage.

Although anemia was only found in 18.62% of the patients, its incidence increased as the GFR decreased. As far as its etiology, we found an absolute iron deficiency in 23.0% and a functional deficiency in 9.6% of the patients, a relatively low figure compared with other international reports (16, 17). Folic acid deficiency only occurred in 0.74%, and vitamin B12 deficiency in 11.9%, mainly affecting stages 3 and 4. High PPI consumption is likely the cause in this group of patients, although it has not been found to be important in patients with CKD on dialysis (22). Hyperparathyroidism affected 56.30% of the anemic patients, and its prevalence was higher at lower GFRs, which reflects late CKD diagnosis and a lack of specialist appointments in previous years. Similar data were reported in other observation studies, highlighting the importance of vitamin D deficiency, early diagnosis and appropriate treatment according to the GFR value (23, 24).

We conclude that anemia affects a significant percentage of patients with CKD and different variables contribute to its etiology. These should be evaluated in all patients with CKD, regardless of their GFR, thus contributing to appropriate treatment. Absolute and functional iron deficiencies also affect CKD patients, as a whole, often requiring the use of iron, which should ideally be administered parenterally (25).

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Table 2. *Characteristics of patients with anemia, according to the CKD stage. The CKD 1 category is excluded, as only one patient had anemia.*

Characteristic	CKD				P*
	2 n=9	3 n=80	4 n=33	5 n=12	
Age, median - IQR	48.0 (25.0 – 73.0)	66.0 (31.0 – 73.0)	64.0 (34.0 – 74.0)	59.5 (40.0 – 67.5)	0.468
Sex, n - % Female Male	 6 (8.0%) 3 (5.0%)	 45 (60.0%) 35 (58.3%)	 15 (20.0%) 18 (30.0%)	 8 (10.7%) 4 (6.7%)	NA
Hemoglobin, median - IQR	10.7 (10.3 – 11.6)	10.5 (9.1 – 11.4)	10.7 (9.4 – 11.4)	9.5 (8.1 – 10.7)	0.427
Serum iron, median – IQR	24.0 (19.8 – 56.1)	39.4 (15.9 – 56.2)	48.0 (27.9 – 59.0)	54.5 (22.0 61.5)	0.522
Ferritin, median – IQR	25.7 (6.7 – 98.0)	28.0 (3.5 – 62.0)	52.1 (9.3 – 130.0)	66.6 (32.4 – 152.0)	0.015
% transferrin sat, median – IQR	7.9 (5.9 – 17.5)	12.1 (4.2 – 20.2)	18.1 (7.9 – 25.6)	18.7 (12.8 – 22.9)	0.024
Iron deficiency, n - % Absolute Functional No deficiency	 3 (9.7%) 1 (7.7%) 5 (5.5%)	 21 (67.8%) 8 (61.5%) 51 (56.0)	 6 (19.4%) 2 (15.4%) 25 (27.5%)	 0 (0.0%) 2 (15.4%) 10 (11.0%)	NA
Vit. B 12 deficiency NO YES	 8 (6.7%) 1 (6.3%)	 71 (59.7%) 9 (56.3%)	 28 (23.5%) 5 (31.3%)	 11 (9.2%) 1 (6.3%)	NA
PTH, median – IQR	47.0 (44.3 – 72.8)	63.2 (39.9 – 90.6)	90.0 (81.1 – 141.5)	191 (117.0 – 265.0)	0.001
Vitamin D, median - IQR	20.6 (17.1 – 26.6)	27.1 (21.4 – 35.0)	26.3 (20.5 – 35.5)	13.1 (10.4 – 16.5)	0.021
IQR: interquartile range. *Wilcoxon.					

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