Diabetes & Metabolic Syndrome: Clinical Research & Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Iron deficiency in chronic kidney disease patients with diabetes mellitus

Nicolas Roberto Robles[d,*], Juan Lucio Ramos[a], Edgar Chavez[d], Boris Gonzalez Candia[d], Miguel Angel Bayo[d], Antonio Cidoncha[b], Juan Lopez Gomez[c], Juan Jose Cubero[d]

[a] Servicio de Medicina Interna, Hospital Infanta Cristina, Badajoz, Spain
[b] Servicio de Analisis Clínicos, Hospital de Don Benito-Villanueva de la Serena, Spain
[c] Servicio de Analisis Clínicos, Hospital Infanta Cristina, Badajoz, Spain
[d] Servicio de Nefrologia, Hospital Infanta Cristina, Badajoz, Spain

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Iron deficiency
Diminished iron availability
Diabetes mellitus
Chronic kidney disease
Anemia

ABSTRACT

Backgrounds: Iron deficiency has been studied extensively in patients with chronic kidney disease on hemodialysis therapy. However, few studies looked at iron treatment in the non-dialysis chronic kidney disease population.
Methods: Five hundred and eighty patients were studied (247 were diabetic persons). Patients were divided into 4 groups: non-diabetic subjects without CKD, non-diabetic ones with GFR < 60 mL/min, diabetic persons without CKD and diabetic ones with GFR < 60 mL/min). Iron deficiency was diagnosed when serum ferritin level was <100 mg/dl. It was defined as diminished iron availability when ferritin was above 100 mg/dl and serum transferrin saturation (TSAT) was <20%.
Results: Anemia was more frequent in the diabetic CKD patients group (52.4%, $p < 0.001$). Anemia prevalence was also higher in all CKD patients as well as in diabetic patients compared with non-diabetic ones. Iron deficiency was more frequent in diabetic patients. Among CKD diabetic patients the prevalence of iron deficiency was higher than in non-diabetic CKD ones. Diminished iron availability prevalence was higher in non-diabetic patients. Logistic regression analysis showed that only sex and diabetes mellitus were independently associated with iron deficiency.
Conclusions: Anemia was more common in diabetic CKD patients. Diabetes mellitus was independently associated with iron deficiency. Surprisingly, diminished iron availability was not more frequent in diabetic patients. The physio-pathological mechanisms that could explain these findings remain to be elucidated.

1. Introduction

Iron deficiency has been studied widely in patients with chronic renal failure on hemodialysis treatment. However, few studies looked at iron deficiency in the non-dialysis chronic renal disease population [1]. Hsu et al. analyzed the relationship in the community among CKD, anemia, and iron deficiency in the Third National Health and Nutrition Examination Survey (1988–1994) and found that individuals with CKD and low iron index values (serum ferritin and transferrin saturation [TSAT]) often have lower hemoglobin (Hb) concentrations. This relationship was most apparent with ferritin levels less than 25 ng/mL, whereas there was no threshold for TSAT [2].

The prevalence of anemia increases with ageing, affecting ~10% of the general population ≥65 years of age [3]. However, the prevalence of anemia in patients with diabetes could be doubled this figure [4]. In other words, diabetes mellitus is more prevalent among people with anemia and CKD than those with CKD and a normal Hb [5]. Anemia in patients with diabetes is likely to be related to renal insufficiency. Anemia associated with erythropoietin (EPO) deficiency can occur early in diabetic nephropathy before the onset of advanced renal failure, but does not normally occur in non-diabetic renal disease of similar severity [6]. However, it has been shown that diabetes increases the risk for developing anemia by two- to threefold when compared to those patients without diabetes and similar renal function, suggesting that diabetes is associated with other underlying causes of anemia in addition to renal impairment and EPO deficiency [7]. In addition to true iron deficiency, many CKD patients have functional iron deficiency, characterized by impaired iron release

* Corresponding author at: Unidad de Hipertensión Arterial, Hospital Infanta Cristina, Carretera de Portugal s/n, 06070, Badajoz, Spain.
E-mail address: nrrobles@unex.es (N.R. Robles).

http://dx.doi.org/10.1016/j.dsx.2018.05.018
1871-4021/

from body stores that is unable to meet the demand for erythropoiesis (also called reticuloendothelial cell iron blockade or diminished iron availability).These patients have low serum transferrin saturation (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores) [8]. This problem seems to be related with inflammation [9], and it has been reported that long-term exposure to oxidative stress in DM induces chronic inflammation [10].

We have tried to evaluate the respective roles of true iron deficiency and chronic inflammatory status (which, in turn, produces functional iron deficiency) in the pathogenesis of anemia in pre-dialysis diabetic CKD patients.

2. Design and methods

Five hundred and eighty patients were studied: they were 356 males and 224 females, mean age was 64.6 ± 10.3 years. They were recruited in the nephrology outpatient clinic at the hospital. Two hundred and forty seven subjects were diabetic persons. Only Caucasian patients were included in the study. Those patients with previous hematological diseases, thalassemia or other familiar anemia, or macrocitosis at the basal analysis, were excluded. Patients were divided into 4 groups: non-diabetic patients without CKD, non-diabetic subjects with GFR < 60 mL/min, diabetic persons without CKD and diabetic ones with GFR < 60 mL/min. The characteristics of each group are shown in Table 1. Informed consent was obtained from all individual participants and the study design was approved by the hospital Ethics Committee.

Serum cystatin C was measured using a BNII nephelometer (Dade Behring Inc., Deerfield, IL, USA) that used a particle-enhanced immunonephelometric assay (N Latex Cystatin-C). The assay range is 0.195 to 7.330 mg/L, with the reference range for young healthy individuals reported as 0.53 to 0.95 mg/L. The cut point for the highest quartile of serum cystatin distribution was 1.05 mg/L and this was the limit used to define high plasma cystatin levels. GFR was estimated from serum creatinine using the CKD-EPI equation [11]. The Hoek formula was used to estimate GFR from cystatin C [12]. It was considered as normal serum creatinine <1.4 mg/dl for males and <1.2 mg/dl for females. Decreased estimated GFR was defined as a value <60 mL/min/1.73m^2. Urinary albumin excretion was measured in 24 h urine collection and patients were categorized using KDIGO definitions [5].

Ferritin was analyzed by turbidimetry using the ADVIA Chemistry Ferritin assay (Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA). Transferrin was analyzed by turbidimetry using the ADVIA Chemistry TRF Transferrin assay (Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA). Blood iron was analyzed by colorimetry after complexing with ferrozine (Advia Chemistry Iron Ferrozina II Gen, Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA). Iron deficiency was diagnosed when plasmatic ferritin was <100 mg/dl following the European Best Practice Guidelines on Anemia management [13]. It was defined as diminished iron availability when ferritin was above 100 mg/dl and serum transferrin saturation (TSAT) was < 20%.

Results are expressed as mean ± 1 standard deviation. All statistical tests were two-sided. For comparisons between groups, Student "*t*" test for paired samples or ANOVA test was used for continuous variables and Chi-square test for categorical variables (a complementary Fischer exact test was performed when Chi-square test was about statistical significance). For variable without normal distribution Mann-Whitney "*u*" test or Kruskal-Wallis test were used to compare values. These parameters have been expressed as median (IR, interquartilic range). The statistical analysis was developed with the package SPSS 21.0.

3. Results

Anemia was more frequent in diabetic CKD patients group (52.4%, 95%CI 44.2–60.6) than in any of the other groups ($p < 0.001$, Chi-square test). Anemia prevalence was also higher in all CKD patients ($p < 0.001$, Chi-square test) as well as in diabetic patients compared with non-diabetic ones ($p < 0.001$, Chi-square test). Among CKD patients, anemia was also more prevalent in diabetic subjects ($p = 0.045$, Chi-square test). All values are shown in Table 2 and Fig. 1.

Table 1
Group Characteristics.

	Without DM		DM		
	Non CKD	CKD	Non CKD	CKD	Units
Age*	61.0 ± 8.3	67.7 ± 9.9	60.5 ± 10.1	68.6 ± 10.7	ys.
Male sex	55.8 (48.5–62.8)	61.8 (53.9–69.2)	64.4 (54.7–73.0)	66.4 (58.4–73.6)	%
Creatinine	0.86 (0.70–1.01)	1.90 (1.48–2.41)	0.90 (0.70–1.04)	2.0 (1.57–2.50)	Mg/dl
GFR	88.0 (71.1–103)	36.2 (25.9–45.9)	87.7 (66.6–109)	32.5 (23.9–42.4)	Ml/mi
Cystatin C	0.87 (0.75–1.02)	1.93 (1.53–2.29)	0.91 (0.71–1.04)	1.94 (1.60–2.37)	Mg/l
Hb	14.5 ± 1.50	13.1 ± 1.94	14.3 ± 1.78	12.6 ± 1.82	g/dl
Fe	83.0 (69.0–101)	69.5 (51.3–87.8)	72.0 (55.0–94.3)	70.0(54.0–83.0)	µg/dl
Ferritin	92.0 (50.0–153)	94.0 (43.7–193)	73.0 (35.0–128)	74.0 (39.2–160)	µg/l
Siderofilin	264 ± 37.4	243 ± 45.7	284 ± 55.1	251 ± 54.9	mg/dl
TSAT	24.9 (19.7–30.6)	22.2 (15.8–30.1)	20.4 (14.3–26.9)	21.6 (15.6–26.2)	%
Fe suppl.	96.7 (94.2–98.2)	3.30 (1.85–5.82)	92.7 (88.8–95.3)	7.29 (4.66–11.2)	%
ESAs	99.6 (97.6–99.9)	0.43 (0.08–2.40)	92.5 (89.3–94.9)	7.47 (5.15–10.7)	%
ACEI/ARB	91.2 (86.1–94.5)	96.7 (92.5–98.6)	97.0 (91.6–99.0)	98.6 (95.1–99.6)	%
P	3.5 ± 0.5	3.3 ± 0.7	3.2 ± 0.6	3.6 ± 0.8	mg/dl

Age was signficantly higher in CKD (diabetic or non diabetic) patients ($p < 0.001$, Anova test, Bonferroni analysis).
Creatinine and cystatin C were also higher in CKD (diabetic or non diabetic) patients ($p < 0.001$, Kruskal-Wallis test).
GFR (glomerular filtration rate) was lower in CKD (diabetic or non diabetic) patients ($p < 0.001$, Kruskal-Wallis test).
Hb (hemoglobin) was lower in CKD (diabetic or non diabetic) patients ($p < 0.001$, ANOVA test).
Serum iron was higher in non diabetic non CKD patiens ($p < 0,001$; Mann-Whitney test).
Ferritin was lower in diabetic non CKD patients ($p = 0.033$, Mann-Whitney test).
Siderofilin was higher in diabetic non CKD patients ($p = 0.032$, ANOVA test; the Bonferroni analysis showed that the difference was significant only between diabética and non diabetic CKD patients, $p = 0.029$).
TSAT was higher in non diabetic non CKD subjects ($p = 0.007$, Mann-Whitney test).
ESAs: Erytropoiesis stimulating agents. Fe suppl: Iron supplements.
ACEI/ARB were less frequent in non-diabetic non-CKD patients ($p = 0.008$, square Chi test).

Please cite this article in press as: N.R. Robles, et al., Iron deficiency in chronic kidney disease patients with diabetes mellitus, Diab Met Syndr: Clin Res Rev (2018), https://doi.org/10.1016/j.dsx.2018.05.018