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RENAL ANEMIA - RISK FACTORS  
FOR CARDIOVASCULAR DISEASE  
AND CHRONIC KIDNEY DISEASE  
-ABSTRACT-

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## Introduction

Anemia, a common complication of chronic kidney disease (CKD), occurs early, still in its early stages, and is associated with accelerating decline in glomerular filtration rate (GFR).

Cardiovascular disease (CVD) are the leading cause of mortality and morbidity in patients with CKD. Heart failure (HF), ischemic heart disease (IHD) and left ventricular hypertrophy (LVH) have a high prevalence in patients with CKD. Anemia is a common feature in patients with CKD and CVD, leading to a decline in GFR, worsening cardiac dysfunction and increased mortality.

Correction of anemia is associated with improved exercise tolerance, physical activity, improving cardiac function and slowing GFR decline and increasing the time to initiation of renal replacement therapy, but the treatment of anemia in these patients is strictly individualized.

According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD was defined as functional or structural kidney abnormalities lasting more than 3 months. CKD was classified according to GFR into 5 stages: Stage 1 GFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>, stage 2 GFR between 60-89 mL/min/1.73 m<sup>2</sup>, stage 3a GFR between 45-59 mL/min/1.73 m<sup>2</sup>, stage 3b GFR between 30-44 mL/min/1.73 m<sup>2</sup>, stage 4 GFR 15-29 mL/min/1.73 m<sup>2</sup> and stage 5 GFR  $<15$  mL/min/1.73 m<sup>2</sup>. According KDIGO diagnosis of anemia is formulated at an Hb below 13 g/dl in men and below 12 g/dl in women.

An appropriate management of anemia, CKD and CVD may reduce hospitalization, can improve quality of life and reduce mortality in these patients.

*Keywords: Chronic kidney disease (CKD), anemia, cardiovascular disease (CVD), glomerular filtration rate (GFR), heart failure (HF), cardio-renal-anemia (CRA) syndrom*

## GENERAL CONTENT

Pathogenesis of anemia in CKD is multifactorial, mainly including EPO and iron deficiency and inflammatory status. Stimulating of production of EPO is activated by transcriptional factors induced by hypoxia (HIF). The presence of diabetes, the development of secondary HPT and inflammation are contributory factors to worsening anemia and reduced response to exogenous EPO administration. Knowledge of the factors and mechanisms that contribute to the development of anemia in chronic kidney disease is of fundamental importance since their correction can improve the degree of anemia and thus slow the progression of CKD.

Anemia can accelerate the progression of CKD by hypoxia, oxidative stress and interstitial fibrosis. Hypoxia and oxidative stress stimulates the production of extracellular matrix by fibroblasts. Anemia and inflammation in patients with CKD are associated with reduced response to EPO therapy and the introduction of medication with an anti-inflammatory and antioxidant role may improve anemia and reduce the decline in GFR. EPO treatment can slow the progression of CKD both by correcting anemia and the antioxidative and antiapoptotic effects.

CVD is the leading cause of death worldwide, with high prevalence in patients with CKD. The presence of anemia, regardless of the stage of CKD, is associated with a poor prognosis and increased mortality. Increased cardiac output secondary to anemia is a maladaptive response in patients with CKD as a result of development of myocardial hypertrophy and ventricular dilation. The relationship between anemia and CVD resulting from structural and functional alterations of the left ventricle: LVH, cardiomyopathy, IHD and HF.

Anemia is an important predictor of adverse outcome in patients with HF and is associated with increased serum levels of amino-terminal natriuretic peptide (NT-proBNP). NT-pro-BNP, marker of acute cardiac decompensation, synthesized in response to increased pressure and volume overload, is a predictor of cardiovascular events and mortality. Hypoxia contributes to the progression of atherosclerosis lesions and increased cardiovascular risk and renal anemia is associated with increased frequency and severity of cerebral ischemic events. The three conditions : CKD, anemia and CVD are linked in the complex called cardio-renal-anemia syndrome (CRA) under which the three factors influence each other.

Appropriate management of anemia is a way to break the vicious circle of CRA syndrome. Correction of anemia with EPO or iron preparations may improve LVH,

ejection fraction (EF), NYHA functional class (New York Heart Association) and decrease the need for diuretics, can stabilize and even increase GFR and reduce the duration of hospitalization. Correction of renal anemia is crucial in preventing the progression of HF. In the absence of correction of anemia in HF become ineffective all other therapeutic measures.

EPO therapy is initiated in patients with CKD at Hb values below 10 g/dl after exclusion of other causes of anemia and achieve the optimal balance of iron for erythropoiesis. Individualization and dose adjustment for EPO is recommended in order to reduce the risk of thrombotic events and associating Hb variability which increased cardiovascular risk and reduce survival. Administration of red cell mass should be avoided whenever possible, especially for patients undergoing a kidney transplant. New therapeutic agents to stimulate erythropoiesis may represent alternative therapies in patients with non-responsive anemia to EPO administration.

## **PERSONAL CONTRIBUTION**

### **PURPOSE AND OBJECTIVES OF RESEARCH**

#### **The purpose of research**

Consists in studying the influence of renal anemia on cardiac function and progression of CKD.

#### **The main objective**

Assessing the role of renal anemia in CVD development and progression of CKD.

#### **Secondary objectives**

1. Establishing the prevalence of renal anemia in patients with CKD.
2. Evaluation of importance of correcting renal anemia and impact on progression of CKD and CVD.
3. Study of the influence of renal anemia and associated risk factors on survival in patients with CKD.

## **MATERIAL AND METHOD**

### **The study population**

We included 165 patients with CKD stages 3-5 monitored outpatient or hospitalized in the Nephrology Clinic of the Emergency County Hospital Craiova. A group of 96 patients had anemia and the control group included 69 patients without anemia.

### **Inclusion and exclusion criteria**

*Inclusion criteria were:*

- patients with CKD stages 3 to 5 whose eGFR was below 60 ml/min/1,73 m<sup>2</sup>
- kidney transplant patients whose eGFR was below 60 ml/min/1,73 m<sup>2</sup>
- patients on renal function replacement therapy by hemodialysis or peritoneal dialysis

*Exclusion criteria were:*

- lack of patient's written consent to participate in this study
- other causes of anemia (deficiency of vitamin B12, folic acid, hemolytic anemia, cancer, infections and blood loss from any cause).
- allergic reactions to erythropoietin

## **RESULTS**

### **Demographic, clinical and laboratory characteristics**

The gender distribution of patients: Study group: 53 (55.20%) women and 43 (44.80%) men. Control group: 19 (27.53%) women and 50 (72.47%) men. Mean age of patients with anemia was 58.33 ± 15.16 years and of those without anemia was 59.09 ± 13.23 years (95% CI: -5.237 to 3.730, p = 0.740). Initiation of dialysis modality: 79.16% on central venous catheter, in 12.50% of patients initiated on peritoneal catheter and 8.34% of patients initiated on arterio-venous fistula.

### **Establishing the prevalence of renal anemia in chronic kidney disease**

Between Hb level and age there was a statistically significant correlation. The prevalence of anemia was higher in women compared to men, women showing a 2-fold higher risk of developing anemia than men (OR = 2.005, p = 0.0001) Anemia was more severe in women than male (10.34 ± 2.04 g / dl versus 11.11 ± 2.62 g / dl, 95% CI: -1.5125 to 0.0315, p = 0.041). Type nephropathy did not significantly influence the presence or severity of anemia (p > 0,05).

The prevalence of anemia increased with GFR decline from 18.52% in stage 3 to 72.73% in stage 5, the highest prevalence of anemia was observed in patients on

hemodialysis (82.46%). In patients who received a renal graft prevalence of anemia was 33.33%. Comparing the average level of Hb in patients in stage 5 with patients in stage 5HD and 5PD respectively, there were no statistically significant difference ( $10.07 \pm 3.65$  g/dl versus  $10.43 \pm 4.94$  g/dl,  $p=0.62$  and respectively  $10.07 \pm 3.65$  g/dl versus  $9.31 \pm 2.11$  g/dl,  $p=0.24$ ). Prevalence and severity of anemia was higher in incident dialysis patients compared with those prevalent.

When initiating renal replacement therapy by dialysis prevalence of anemia was 95.8%, while prevalent patients had a prevalence of anemia of 67.7% ( $\text{Chi}^2 = 27.96$ ,  $p = 0.0001$ ). Hb level was significantly lower in incident dialysis patients compared with those prevalent ( $8.11 \pm 2.27$  g/dl versus  $10.29 \pm 2.86$  g/dl, 95% CI: - 9.037 to 3.051,  $p=0.0001$ ). Use of a temporary vascular access for hemodialysis was associated with a higher risk of developing anemia compared with those with permanent vascular access (OR = 1.38 versus OR = 0.72,  $p = 0.02$ ).

Also, dialysis patients with central venous catheter had a Hb level significantly lower than those on peritoneal dialysis ( $8.41 \pm 2.37$  g/dl versus  $10.48 \pm 2.22$  g/dl, 95% CI: - 3.432 to 0.708,  $p = 0.002$ ) or arteriovenous fistula ( $8.41 \pm 2.37$  g / dl versus  $10.11 \pm 1.66$  g / dl, 95% CI: -2.742 to 0.658,  $p=0.004$ ) . Between Hb levels in peritoneal dialysis patients and hemodialysis patients on arteriovenous fistula there were no statistically significant differences ( $10.48 \pm 2.22$  g/dl versus  $10.11 \pm 1.66$  g/dl, 95% CI: - 1.348 to 0.657,  $p=0.474$ ).

#### *Anemia and nutritional status*

Malnutrition in patients with CKD was associated with a significantly higher risk of developing anemia compared with patients without malnutrition (OR=4.672, 95% CI: 1.089 to 20.041,  $\text{Chi}^2=5.502$ ,  $p=0.015$ ). Anemia was more severe in patients with malnutrition compared to those without ( $9.19 \pm 2.71$  g/dl versus  $10.93 \pm 2.33$  g/dl, 95% CI: -3.004 to 0.473,  $p=0.007$  ). The presence of obesity was associated with a lower risk of developing anemia compared with patients without obesity (OR=0.419, 95% CI: 0.234-0.750,  $\text{Chi}^2 = 9.240$ ,  $p = 0.002$ ). Serum Hb was positively correlated with BMI ( $r = 0.315$ ,  $p = 0.0001$ ).

*Anemia and inflammation:* the prevalence of anemia was higher in patients with serum ferritin values above 500 ng/ml compared to those below 500 ng/ml (contingency coefficient 0.275,  $p=0.001$ ). A protein C reactive (CRP) level greater than 3 mg/dl was associated with a higher prevalence of anemia compared with patients with CRP less than 3 mg / dl (contingency coefficient 0.239,  $p=0.001$ ).

*Anemia and secondary hyperparathyroidism:* an intact parathormone (iPTH) value above 300 pg/ml were associated with a higher prevalence of anemia compared with iPTH below 300 pg/ml (contingency coefficient 0.333,  $p=0.0001$ ). Hb level was negatively correlated with iPTH ( $r = -0.483$ ,  $p = 0.0001$ ). The presence of secondary HPT was an independent risk factor for the development of anemia (OR = 1.971, 95% CI: 1.503 to 2.584,  $p = 0.0001$ ). Student t test for comparison of averages showed lower Hb values in patients with secondary HPT compared to those without secondary HPT ( $10.33 \pm 2.08$  g/dl versus  $13.11 \pm 1.84$  g/dl, 95% CI: -3.717 to 1.834,  $p=0.0001$ ).

### **Study of the influence of renal anemia on chronic kidney disease and cardiovascular disease**

#### *Study of the influence of renal anemia on chronic kidney disease*

In the presence of anemia, renal damage was more severe. Looking through a logistic regression model anemia influence on the severity of CKD was observed that the presence of anemia was associated with a significantly higher risk of having a GFR below 15 ml/min/1.73 m<sup>2</sup> (OR = 5.907, 95% CI : 2.973 to 11.734,  $p=0.0001$ ) compared with patients without anemia. Residual diuresis in patients with anemia at baseline was lower than in patients without anemia ( $1201.04 \pm 882.99$  ml versus  $1836.96 \pm 918.10$  ml, 95% CI: - 715.71 - 156.11,  $p=0.002$ ); between diuresis and Hb level there is a direct, statistically significant relationship ( $r = 0.300$ ,  $p = 0.0001$ ). Serum Hb was negatively correlated with proteinuria ( $r = -0.243$ ,  $p = 0.008$ ). Mean Hb was lower in patients with macroalbuminuria compared to those without ( $10.10 \pm 2.45$  g/dl versus  $10.98 \pm 2.37$  g/dl,  $p = 0.032$ ).

#### *Study of the influence of renal anemia on cardiovascular disease*

LV systolic function assessed by LVEF was lower in patients with anemia than those without anemia ( $48.47 \pm 7.61\%$  versus  $51.55 \pm 6.24\%$  (95% CI: - 5.2834 to 0 , 8742,  $p=0.006$ ). Prevalence of systolic cardiac dysfunction was higher in patients with anemia than those without anemia (39.6% versus 17.4%), anemia represents a risk factor for the development of cardiac systolic dysfunction (OR=1.507, 95% CI: 1.187 to 1.914,  $p=0.002$ ). Between Hb and LVEF there was a correlation statistically significant ( $r = 0.273$ ,  $p=0.001$ ). Analysis by logistic regression the influence of Hb levels on systolic cardiac dysfunction and associated ROC curve demonstrates a valid logistic model (95% CI: 0.587 to 0.766,  $p=0.0001$ ). Logistic regression analysis of the influence of Hb levels on cardiac diastolic dysfunction do not show statistical significance (95 % CI: 0.427 to 0.607,  $p=0.712$ ).



47.88% of studied patients with CKD were diagnosed with HF. Anemia was an independent risk factor for the development of HF (OR = 2.12, 95% CI: 1.419 to 3.169,  $p=0.0001$ ). Anemia was more severe in patients with symptoms of HF compared those without manifestations of HF (Hb values were  $9.84 \pm 2.24$  g / dl versus  $11.63 \pm 2.24$  g / dl,  $p = 0.0001$ , 95% CI = -2.4872 to 1.1055). After logistic regression analysis for Hb levels influence on development of HF resulted a valid logistic model ( $p = 0.0001$ ). The prevalence of anemia was 43% in patients without symptoms of HF, 65% in patients with NYHA class II, 79.25% in patients with NYHA Class III and 66.67% in NYHA class IV.

The risk of developing LVH was higher in patients with anemia than those without anemia (OR = 1.311, 95% CI = 0.989 -1.737,  $p = 0.035$ ). Between the Hb level and interventricular septum (IVS) and posterior wall of the left ventricle (PWLV) respectively there was a statistically significant negative correlation.

10 (14.49%) patients without anemia and 32 (33.33%) of patients with anemia developed thrombotic events in 12 months and the risk was higher for patients with anemia (OR = 1.562,  $p = 0.042$ ). The prevalence of IHD was lower in patients without anemia compared to those with anemia (21.73% versus 46.87%,  $p = 0.040$ ), but the severity of anemia did not differ with the presence of IHD ( $10.78 \pm 2.52$  g / dl versus  $10.77 \pm 2.21$  g / dl,  $p = 0.977$ ).

### **Evaluation of importance of correcting renal anemia and its impact on chronic kidney disease progression and cardiovascular disease**

#### *General characteristics*

The lot of anemic patients was divided into two subgroups, group A - 49 patients who did not received treatment for anemia and group B - 47 patients with anemia who received treatment. From group B, 31 (66%) received EPO, 6 (12.76%) had received only iron, 10 (21.24%) had received both EPO and iron, for 11 (23%) of patients was imposed red blood cell transfusions.

#### *Evaluation of importance of correcting anemia and impact on progression of CKD*

Increasing of GFR was higher in the treated compared with untreated patients ( $9.97 \pm 0.83$  ml/min/1,73 m<sup>2</sup>/year versus  $7.70 \pm 1.02$  ml/min/1,73 m<sup>2</sup>/year,  $p=0.005$ ). In the group of patients whose GFR decreased, the differences are not significant between the two groups. Analysing the serum creatinine level after 12 months, we observed a rise in serum creatinine 0.74 mg/dL /year in untreated patients and a decrease in serum creatinine 0.18 mg/dL/year in treated patients, but in both cases the differences were not statistically significant ( $p > 0.05$ ).

The significant influence of ERI on renal function was highlighted following a binary regression model showing a 2.7 times higher risk of having a GFR below 15 ml/min/1,73 m<sup>2</sup> for patients with EPO resistance (OR=2.701, p=0.009). The evolution of residual diuresis during the 12 months of monitoring showed a greater reduction in diuresis in untreated patients compared to those treated (268.76 ± 194.17 versus 166.37 ± 103.32 ml, p = 0.002).

*Evaluation of importance of correcting renal anemia and its impact on CVD*

The prevalence of hypertension after 12 months did not differ significantly with therapy of anemia: increased with 2.05% in patients in group A and 4.28% respectively in patients in group B (p < .05).

Among patients with LVEF increased, this increase was higher in treated compared with untreated patients (9.53 ± 0.22% versus 8.93 ± 0.28%, p = 0.0001). Among patients in the LVEF decreased, the decrease was significantly greater for the untreated (-10.03 ± 0.42% vs. -7.93 ± 0.41, p = 0.0001). But there were patients with LVEF remained unchanged in the treated group (29.26%) and in untreated (23.91%). Patients who maintained Hb above 11 g/dL at 12 months showed a slight increase in LVEF (2.72 ± 0.51%, p=0.105), but LVEF in patients with Hb level below 11 g/dL declined by 3.56 ± 0.38%, p=0.018.

The prevalence of IHD in patients treated with EPO decreased from 46.3% at baseline to 31.7% after 12 months (contingency coefficient=0.452, p=0.052) and in those treated did not change significantly after 12 months (47.2% versus 45.5%, p=0.541).

The prevalence of HF after 12 months decreased in patients treated with EPO (65.9% versus 46.3%, p = 0.025) and significantly increased in patients with anemia untreated (58.2% versus 70.90%, p = 0.045). By entering into a logistic regression model EPO resistance (ERI) and HF was observed a 7.6 times higher risk of developing HF in patients with EPO resistance (OR = 7.607, p = 0.004). Patients who developed thrombotic events require higher doses of EPO than those without thrombotic events. ERI was higher in patients who developed thrombotic events compared with those without thrombotic events (0.066 ± 0.016 mcg/kg/week/g Hb versus 0.046 ± 0.029 mcg/kg/week/gHb, 95% CI: 0.001 to 0.038 p=0.034). A binary regression model conducted for evaluate the influence of resistance to EPO on the risk of cardiovascular events showed a statistically significant relationship (OR=4.05, p=0.44).

### **Study of the influence of renal anemia and associated risk factors on survival in patients with chronic kidney disease.**

The risk of death did not differ significantly with the presence of anemia (OR = 1.210, 95% CI: 0.821 to 1.782). Survival analysis of patients from treated group compared with untreated also show no significant differences in risk of death. In the presence of anemia serum phosphorus levels above 4.5 mg/dL, GFR below 15 ml/min/1,73 m<sup>2</sup> and macroalbuminuria, were associated with a higher risk of death (p <0,05).

Patients with HF compared with those without HF had a significantly higher risk of death (OR = 2.094, 95% CI: 1.650 to 2.657, p=0.001) independently of presence of anemia. Patients with symptoms of HF had a better survival compared with those with HF NYHA class II (p = 0.051), NYHA class III (p = 0.009) and NYHA class IV (p = 0.0001).

### **CONCLUSIONS**

1. Anemia is a major risk factor for progression of CKD and its correction was associated with improved GFR, but without affecting the level of proteinuria.
2. Anemia is a major risk factor for the development of LVH, ischemic heart disease, cardiac systolic dysfunction and HF, correcting them being associated with improved LVEF, reducing the prevalence of IHD and HF, but without affecting LVH.
3. Prevalence of renal anemia increased with declining of GFR, anemia being more severe and more common in women, in incident dialysis patients, especially with central venous catheter, in the presence of malnutrition, inflammation and secondary hyperparathyroidism.
4. Anemia was not an independent predictor for mortality in CKD, but in combination with other risk factors such as macroalbuminuria, hyperphosphatemia, severe renal impairment or HF, has contributed to reduce survival of these patients.
5. Regardless of the cause of anemia in CKD and associated risk factors, early management of this entity is necessary to reduce cardiovascular risk and progression of CKD.