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The Influence of Inflammation Markers on Anemia and Erythropoietin Responsiveness in Hemodialysis Patients in a Dialysis Unit from Romania

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A poor response to recombinant human erythropoietin (rHuEPO) is encountered in up to 15% of hemodialysis patients[1]. Some factors such as iron deficiency, blood loss, vitamin deficiency, aluminum toxicity and underdialysis are known to play a major role in rHuEPO hyporesponsiveness. Even after all these factors are excluded some patients remain anemic suggesting that there are other associated conditions that might influence the treatment of anemia in hemodialysis patients[2-5]. Less attention has been accorded to inflammation and malnutrition. It is well known that uremic patients have an increased immune activation with high levels of proinflammatory cytokines[1,4]. It also has been observed that chronic inflammatory diseases are associated with anemia even in patients with normal kidney function. On the other hand, hemodialysis patients with vascular access infections require higher doses of rHuEPO. This suggests that chronic inflammation can inhibit the process of erythropoiesis either directly by increasing the level of proinflammatory cytokines in bone marrow[1], or indirectly by interfering with iron metabolism[6,7]. The aim of this study is to examine the relationship between anemia, EPO dose and inflammation-malnutrition in hemodialysis patients.

Data from 34 hemodialysis patients treated with rHuEPO were analyzed. Patients with iron deficiency, secondary hyperparathyroidism, blood loss, neoplasia and acute infections were excluded. All patients received intravenous iron supplementation and oral folic acid. C-reactive protein (CRP) levels were measured as a marker of inflammation. EPO dose (U/kg/week) and EPO responsiveness index (EPO/week/hematocrit) were calculated. Serum creatinine and body mass index (BMI) were considered as nutritional markers. Hemoglobin, hematocrit, serum ferritin were measured. Data is presented as mean±SEM.

Table 1: General characteristics of the group

Mean age (years)	54.7 ±1.8
Mean time in dialysis (years)	5.5 ±0.6
Mean Kt/V	1.4 ±0.2
Mean BMI (kg/m^2)	22.9 ±1.1
Primar nephropathy	
Glomerular diseases	10 (29.41%)
Diabetic nephropathy	2 (5.88%)
Nephroangiosclerosis	4 (11.76)
Polycystic kidney disease	7 (20.58%)
Others	8 (23.52%)

Hemoglobine g/dl	10.3 ±0.2
Serum iron	116.6 ±3.6
Serum ferritin ng/ml	337.7 ±24.5
CRP mg/l	7.5 ±1.3
Serum creatinine mg/dl	9.5 ±0.3
EPO U/week	5588.2 ±24
EPO U/kg/week	82.2 ±7.1
EPO U/week/hematocrit	182.7 ±15.9

Mean hemoglobin was 10.3±0.2 g/dl, mean EPO dose was 82.8±7.1 U/kg/week and mean Kt/V was 1.5±0.5. Patients were divided in two groups: group A (CRP<1 mg/l), and group B (CRP>1 mg/l). Hemoglobin was higher in patients from group A than in group B (11.1±0.5 vs. 10.1±0.2 g/dl, p=0.067, NS); however administered EPO dose (56.3±18.6 vs. 93.8±7.2 U/kg/wk, p<0.05) as well as EPO responsiveness index (103.4±30.7 vs. 207.1±16.1, p=0.0041) were significantly lower in group A compared to group B. Patients with hemoglobin<11 g/dl had higher levels of CRP (9.8±1.6 vs. 2.0±0.9 mg/l, p=0.00314), received higher EPO dose (100.7±8.2 vs. 47.1±6.7 U/kg/wk, p=0.0004) and had worse EPO response expressed by higher EPO responsiveness index (222.3±16.1 vs. 87.6±12.8, p<0.05) compared to patients with hemoglobin>11 g/dl. CRP levels displayed an inverse correlation with hemoglobin (R 0.421, p=0.0132), a positive correlation with administered EPO dose (R 0.573, p=0.0005), and EPO responsiveness index (R 0.638, p<0.0001).

The level of serum creatinine as a nutrition marker inversely correlated with CRP (R 0.534, p=0.001) as well as rHuEPO dose (R 0.496, p=0.003) and rHuEPO responsiveness index (R 0.356, p=0.038). Patients from group A (CRP<1 mg/l) had higher levels of serum creatinine (10.73±0.46 mg/dl vs. 9.12±0.33 mg/dl) and required lower doses of rHuEPO compared with those from group B (CRP>1mg/l). No correlations with age, gender, BMI, dose of dialysis or type of membrane were present. Evolution of hemoglobin at 3 and 6 months was strongly predicted by baseline CRP value.

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Table 3: Characteristics of group A compared with group B:

CRP (mg/l)	Hb(g/dl)	rHuEPO U/kg/week	rHuEPO U/week/hematocrit	Serumcreatinine (mg/dl)
< 1 (group A)	11.1±0.5	56.3±18.6	103.4±30.7	10.7±0.4
> 1 (group B)	10.1±0.2	93.8±7.2	207.1±16.1	9.1±0.3

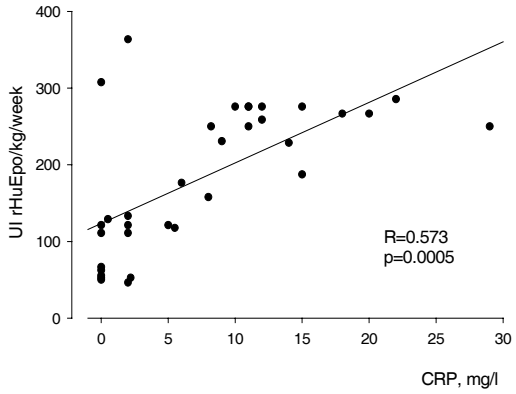

Fig.1: Correlation between CRP and EPO dose

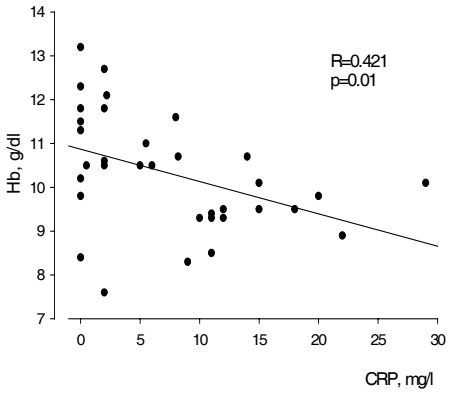

Fig.2: Correlation between CRP and Hb

Table 4: Hemoglobin evolution and EPO dose at 3 and 6 months

CRP (mg/l)	Hb (g/dl) at 3 months	Hb (g/dl) at 6 months	EPO U/kg/week at 3 months	EPO U/kg/week at 6 months
< 1(group A)	11.9±0.6	12.1±0.4	44.3±18.6	42.9±21.6
> 1(group B)	10.2±0.3	9.9±0.4	93.8±7.2	95.4±4.6

Patients with CRP<1 mg/l (group A) displayed an increase in hemoglobin:11.9±0.6 g/dl at 3 months (p=0.016 vs. group B) and 12.1±0.4 g/dl at 6 months (p=0.0036 vs. group B); this allowed EPO dose to be decreased to 44.3±18.6 U/kg/wk at 3 months and 42.9±21.6 U/kg/wk at 6 months (NS), while patients with CRP>1 mg/l maintained a stable hemoglobin:10.2±0.3 g/dl at 3 months and 9.9±0.4 g/dl under similar EPO dose.

In conclusion, there is a strong correlation between anemia and inflammation and malnutrition markers in hemodialysis patients and CRP is a strong predictive factor of EPO responsiveness.

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