



Serum Erythropoietin levels in patients with CKD and anemia on dialysis treatment

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ABSTRACT

A prospective study was conducted evaluating the serum erythropoietin level in patients with chronic renal failure/chronic kidney disease treated with dialysis. A total of 86 patients treated with hemodialysis and 14 patients treated with peritoneal dialysis (PD) were included. An analysis was made of the correlations between the serum levels of endogenous erythropoietin with haemoglobin doses of recombinant exogenous erythropoietin, serum creatinine, URR and main renal disease.

The results show that in patients undergoing hemodialysis treatment the level of serum erythropoietin varies from 1,1 to 62,5 U/l and in 29,1% of the patients it is below the reference range. There is no significant difference between the serum erythropoietin levels in patients from both genders. There is no significant difference between serum erythropoietin and haemoglobin, dose of the exogenous epoetin, URR and the main renal disease. An inversely proportional relationship between serum erythropoietin and the level of serum creatinine measured before the beginning of hemodialysis procedure is noticed.

In patients treated with PD the level of serum erythropoietin varies between 2,8 and 68,5 U/l, the average level of serum erythropoietin is significantly higher and the average age and duration of renal replacement therapy is significantly shorter compared to patients on hemodialysis.

We noticed versatile relations between the level of serum erythropoietin and the main markers for chronic renal failure and dialysis treatment. Patients undergoing treatment with PD have higher serum levels of epoetin and better markers for renal replacement therapy.

Key words: erythropoietin, renal anemia, chronic renal failure, chronic kidney disease, dialysis.

I. INTRODUCTION

Chronic renal failure (CRF) is defined in recent years as a medical problem with a large socio-economic significance (9, 13). The frequency of CKD nowadays is more than 1000 to 1 million population.

The most common complication of CRF is renal anemia (6).

The National Health and Nutrition Examination Survey III summarizes data, collected for the period 2007-2010 and states that anemia is two times more frequent in chronic kidney disease (CKD) (15,4%), compared to the general population (7,6%). The frequency increases from 8,4% in CKD I stage to 53,4% in CKD V stage (22).

A deficiency in the erythropoietin (Epo) production has been thought to be the main cause of anemia in patients with end-stage renal disease (ERSD) (5, 7, 10).

Anemia continues to be an important complication in patients with CRF/CKD, regardless of the fact that it can be treated (6). The importance of anemia treatment is connected with reduction in morbidity and mortality due to reduced incidence of left ventricular hypertrophy and consecutive heart failure, a condition now addressed as cardiorenal syndrome (11, 13, 21).

The erythropoietin discovery in 1977 (16) and cloning of the gene responsible for its synthesis in 1985 (12) were followed by initiation of the production of human recombinant erythropoietin, which nowadays is used massively and without limitations for treatment of renal anemia (RA) in all stages of CRF/CKD.

In these patients, anemia does not always induce an appropriate elevation in the serum Epo level. The mechanisms for inappropriately lower serum Epo in ERSD remain unclarified (10).

The recombinant human erythropoietin treatment of anemia in chronic renal failure got



much less cumbersome and risky than in the past, when regular blood transfusion were required. One reason for this uncertainty is the lack of a measurable parameter for inadequate erythropoietin synthesis (5).

There is a large number of papers connected to the treatment of RA with recombinant erythropoietin, but the number of publications discussing the evaluation of serum erythropoietin levels in patients with CRF/CKD is very small.

Interpretation of serum erythropoietin levels in the context of renal insufficiency remains controversial (5) and is addressed in this study, which is focused on evaluation of serum erythropoietin levels in patients with ESRD and evaluation of the relationship with haemoglobin, serum creatinine, iron status and the treatment with recombinant erythropoietin. The study is approved by the Institutional Ethics Committee and is financed by Medical University – Pleven, Bulgaria (Scientific project №2/2022).

II. MATERIAL AND METHODS

A study of the serum erythropoietin level in patients with CKD V stage is conducted, 86 of which are treated with hemodialysis and 14 – with peritoneal dialysis. The group treated with HD includes 50 males (58,1%) at average age 61,6±13,2 years and 36 females (41,9%) at average age 57,7±12,0 years. In the group treated with

peritoneal dialysis there are 8 males at average age 55,2±13,3 years and 6 females at average age 44,3±14,4 years.

The patients underwent treatment of RA with Epoetin alpha. All patients received oral or intravenous iron supplementing drugs and medications for correction of the disturbances in the calcium-phosphate metabolism.

Standard laboratory markers were used. The serum erythropoietin level is tested with solid phased, enzyme-binded hemiluminiscent immunometric test with IMMULITE 2000 Immunoassay Systems – Simens Healthineers. The reference ranges of the serum erythropoietin are from 4,2 to 20,8 U/l. The results are analysed with alternative and variation methods of statistical analysis.

III. RESULTS

Group of patients treated with HD

The average level of serum erythropoietin is 9,2±10,0 U/l, in male patients it is 9,8±10,2 U/l, in females – 8,4±9,7 U/l, the difference is not significant ($p>0,05$). The average level of serum iron, transferrin saturation and serum creatinine at the beginning of hemodialysis procedure are with insignificant differences in patients from both genders. The average values of haemoglobin and URR are small with insignificant differences ($p>0,05$) (tabl. №1).

Table №1. Main laboratory markers, characterizing the severity of anemia, iron status and CKD (n=86).

	Hemoglobin (g/l)	Serum iron (mcmol/l)	TSAT (%)	Serum creatinine at the beginning of HD (mcmol/l)	URR (%)
Female	103,4±17,1	11,4±6,2	25,3±10,6	838±168	68,3±9,2
Male	110,9±18,7	11,7±4,1	26,5±8,6	857±257	63,2±10,6
Total	107,8±18,3	11,6±5,1	26,0±9,4	849±217	65,3±10,3

The level of serum erythropoietin in the evaluated group varies widely from 1,1 to 62,5 U/l. In 25 patients (29,1%) the level is below the reference range of the norm. In most patients – 58/86 the level of serum erythropoietin is within the reference interval, and only in 3/86 it is higher than the reference range of this interval. Comparison of the values of serum erythropoietin with the haemoglobin levels shows that the severity of anemia is equal in three out of the four

subgroups, divided based on the levels of erythropoietin. The group with the highest levels of erythropoietin the average haemoglobin value is equal to the values in other two groups. There is no connection between the serum level of epoetin and the serum iron level. The average level of serum creatinine at the beginning of hemodialysis procedure gradually decreases in the groups with higher serum erythropoietin interval, but also this is not valid for the URR (tabl. №2).



Table №2. Average values of haemoglobin, serum creatinine and creatinine clearance in different levels of serum erythropoietin (n=86).

Serum level of Epo (U/l)	Number of patients	Hemoglobin (g/l)	Serum iron (mcmol/l)	Serum creatinine at the beginning of HD (mcmol/l)	URR (%)
Below 4,2	25	109,7±28,6	13,2±5,3	927±209	62,0±12,3
4,3-12,5	46	109,1±17,3	10,9±4,9	848±218	67,5±9,5
12,6-20,8	12	92,1±21,0	10,1±4,4	733±176	62,6±7,6
Above 20,8	3	109,7±28,6	14,2±7,0	686±178	69,3±4,3

The haemoglobin value in evaluated patients varies from 65 to 149 g/l. Comparison of the average levels of serum erythropoietin in the groups with different level of haemoglobin does not find a connection between the two markers. In patients with most severe anemia the average level

of serum erythropoietin is the highest. There are no significant differences between the levels of serum iron in patients with different severity of anemia. Between haemoglobin and the average dose of the used recombinant erythropoietin (tabl. №3).

Table №3. Values of the serum erythropoietin and doses of recombinant erythropoietin in patients with different severity of anemia (n=86).

Hemoglobin (g/l)	Number of patients	Level of Epo U/l	Serum iron (mcmol/l)	Dose of Epo
65-90	14	13,9±9,2	9,4±5,5	7860±3440
91-110	33	8,9±9,5	10,9±4,3	6300±2280
111-120	20	6,1±5,9	13,2±6,1	3250±2511
Above 120	19	9,5±13,6	12,6±4,5	1370±1570

The treatment of renal anemia with recombinant erythropoietin is performed in 71 from the evaluated 86 patients. The analysis of the relation between the levels of serum erythropoietin and the dose of recombinant erythropoietin shows that the average level of serum erythropoietin is higher in patients who do not receive recombinant erythropoietin compared to patients treated with

recombinant erythropoietin in doses from 9000 UI/weekly. This method of comparison also confirms the back correlation between the haemoglobin level and the dose of applied recombinant epoietin. There is no relation between the dose of the applied exogenous erythropoietin and the serum level of erythropoietin (tabl. №4).

Table №4. Levels of serum erythropoietin and haemoglobin in patients treated and untreated with different doses of recombinant erythropoietin (n=86).

Dose of recombinant erythropoietin (UI/седм.)	Number of patients	Serum erythropoietin (U/l)	Hemoglobin (g/l)
0	15	13,6±16,0	127,2±21,2
2000-3000	20	6,5±5,1	113,2±11,3
4000-6000	24	5,2±2,9	106,8±12,5
7000-9000	24	11,2±11,0	96,0±12,6
9000-12000	3	20,6±7,2	77,5±7,5



Data analysis shows that in the subgroups with higher levels of serum creatinine at the beginning of HD procedure the average level of serum erythropoietin is lower and the differences

between the values in the first and second subgroups and the rest is significant ($p < 0,05$). There is no correlation between the serum creatinine and haemoglobin (tabl. №5).

Table №5. Levels of serum erythropoietin, haemoglobin and URR in different values of serum creatinine at the beginning of hemodialysis procedure (n=86).

Serum creatinine at the beginning of HD (mcmol/l)	Number of patients	Hemoglobin (g/l)	Serum level of Epo (U/l)	URR (%)
Below 700	19	106,1±18,5	12,4±8,7	65,6±13,8
701-800	20	100,9±19,1	12,6±16,8	63,8±9,7
801-900	15	104,6±14,0	8,2±6,1	64,1±11,6
901-1100	25	111,6±17,1	6,0±3,4	67,5±7,9
Above 1100	7	125,3±18,1	4,6±2,8	63,6±5,9

Analysis of the results does not allow us to make a connection between the URR and serum erythropoietin, and the duration of hemodialysis treatment and serum erythropoietin.

There is also no connection between the serum level of erythropoietin and the severity of anemia with the main renal disease (tabl. №6).

Table №6. Levels of serum erythropoietin and haemoglobin in patients with different renal diseases (n=86).

Main renal disease	Number of patients	Hemoglobin (g/l)	Serum level of Epo (U/l)
Hypertensive nephropathy	26	110,4±14,7	6,7±5,4
Chronic glomerulonephritis	23	113,2±18,8	11,5±15,8
Diabetic nephropathy	10	99,3±16,5	8,8±7,2
Chronic interstitial nephritis	9	104,4±17,5	7,7±5,0
Autosomal dominant polycystic kidney disease	7	103,9±16,1	8,7±5,1
Congenital kidney anomalies	5	127,6±6,6	7,2±3,3
Others	6	88,8±22,1	16,4±11,6

II. Comparison between HD and PD.

In patients treated with CAPD the level of serum erythropoietin varies from 2,8 to 68,5 U/l. the average level of serum erythropoietin in patients treated with PD is significantly higher than the levels in patients treated with HD. The average

age and average duration of dialysis treatment in the group treated with PD is significantly smaller (tabl. №7). The markers related to the correction of renal anemia and depuration have completely comparable values.

Table №7. Main data and markers in the groups of patients with CKD treated with HD and PD (n=100).

	Number of patients	Age (years)	Serum level of Epo(U/l)	Hemoglobin (g/l)	Dose Epo (UI/weekly)	Duration RRT (monts)
HD	86	60,0±12,8	9,2±10,0	107,8±18,3	4750±3364	81±75
PD	14	48,9±14,5	23,1±20,3	107,7±12,4	4000±2960	36±37
p	-	<0,01	<0,02	-	p>0,05	<0,01



IV. DISCUSSION

The results from our study show that the average serum erythropoietin levels in hemodialysis patients from both genders are within the reference range. There are insignificant differences between the average levels of haemoglobin, serum iron, TSAT, serum creatinine and URR in males and females in this group. We accept that there is no iron deficiency. We found no publications that make a similar comparison.

Our data shows that in significant number of patients treated with hemodialysis (29,1%) the level of serum erythropoietin is below the reference range of the norm, but the haemoglobin in this patients is not lower than Hb in patients with normal erythropoietin levels. Overall there is no relation between serum erythropoietin and anemia. There is also no relation between serum erythropoietin levels and the levels of serum iron, creatinine and URR.

Publications for measurement of serum erythropoietin levels in patients with CKD are very few (5, 15). The literature review shows that most of them are from the period 1977-2000. Some papers (2, 8, 10, 14) summarize results from evaluation of a very small number of patients.

A.Keto et al. (10) evaluate 18 patients with ESRD and state that in the absence of acute bleeding or hypoxia, the serum erythropoietin level in ESRD was similar to that of normal subjects despite the severe anemia. The serum erythropoietin level in these patients declined to or near the normal value after recovery from acute hypoxic stress. These data suggests that the ability of erythropoietin production is well preserved in ESRD.

According of E. Mady et al. (14) CRF patients were not iron deficient. This coincides with the report of G. Steffensen et al. (23) in which 15 ESRD patients were recruited in the study, all of whom were not iron deficient, regardless of the type of dialysis treatment.

H. Radtke et al. (19) test the level of serum erythropoietin in 135 patients with creatinine clearance from 2 to 90 ml/min and report elevated erythropoietin levels in all subgroups. In patients with creatinine clearance below 40 ml/min they report disproportionately high levels of serum erythropoietin. Our results differ from the cited – the levels of serum erythropoietin are very low in almost 1/3 of the patients.

Another study of 395 patients from T. Fahr et al. (5) reports that patients with glomerular filtration rate below 20 ml/min. have significantly lower haemoglobin level than in healthy patients. Despite that, the erythropoietin levels among them

are identical, which is a „bad indicator for erythropoietin regulation“. The authors report a relation between serum erythropoietin and haemoglobin only when glomerular filtration rate is above 40 ml/min., and also in lower glomerular filtration rates, the serum erythropoietin levels remain disproportionately high. They accept that „Erythropoietin levels are difficult to interpret in the context of renal failure“. Y. Fukushima et al. (8) accept that elevated levels of erythropoietin in patients with severe anemia may be a result of highly elevated levels of epoetin inhibitors.

E. Mady et al. (14) report 40 patients with CRF of hemodialysis treatment, half of which have liver cirrhosis and report that CRF patients without liver cirrhosis had serum epoetin concentration of $6,21 \pm 0,53$ mU/ml, which was significantly higher than in patients having both CRF and liver cirrhosis ($4,32 \pm 0,52$ mU/ml) and no correlation was found between epo and haemoglobin among hemodialysis patients.

C. Seguchi et al. (20) evaluate 67 patients on hemodialysis and found no significant correlation between concentrations of serum epoetin and haemoglobin, but found a significant negative correlation between serum concentrations of epo and iron in hemodialysis patients.

M. Panjeta et al. (18) evaluate 356 patients in all stages of CKD and found out that in patients with CKD II and III grade the median values of serum erythropoietin are significantly higher, whereas in patients with CKD IV and V grade – significantly lower, compared to healthy people. The average levels of serum erythropoietin in all groups are within the reference range.

With non-renal failure anemia serum erythropoietin levels are usually elevated in an effort to compensate for the anemia, and correlations have been made between haemoglobin and serum erythropoietin (24). There are although many cases of non-renal anemia, with inappropriately low erythropoietin levels for the severity of their anemia (1).

The results from our study show that serum erythropoietin is the highest in patients with the lowest haemoglobin levels, but we did not find a correlation between haemoglobin and serum epoetin. We did not find any similar comparisons in other publications.

Our analysis shows that serum erythropoietin is the highest in patients who do not perform treatment with exogenous epoetin and who are with the highest average haemoglobin level. This kind of comparison also is not present in the researched literature. Respectively, we found a



back correlation between haemoglobin and the dose of exogenous erythropoietin.

Our data shows a back correlation between the average levels of serum creatinine measured at the beginning of hemodialysis procedure and the average level of serum erythropoietin. We did not find such an analysis in the literature.

R. McGonigle et al. (15) found out from an evaluation of 60 patients with different stage of CRF, that the average erythropoietin level is slightly elevated and there is no correlation with the serum creatinine level. They also report an exponential increase of the serum erythropoietin when haematocrit decreases below 32%.

K. Morris and M. Coulthard (17) accept that although haemoglobin declines along with glomerular filtration rate, Epo levels change very little as renal function declines; this is against deficiency of Epo being directly attributable to a reduction in renal mass.

We did not find any correlation between the main renal disease and the serum erythropoietin level. The last is not higher in patients with ADPKD, compared to patients with the other chronic nephropathies. M. Chandra et al. (3) found in 12 patients on hemodialysis with ADPKD two times higher average level of serum erythropoietin compared to all other patients, treated with HD.

Y. Fujita et al. (7) conduct a study of 339 type 2 diabetic patients and report that inappropriately low Epo levels were observed in 73% of anemic patients and 59% of anemic patients even without CKD, suggesting that Epo deficiency precedes the onset of CKD in diabetes mellitus.

Our study shows that the average serum erythropoietin levels are significantly higher in patients treated with PD compared to those treated with HD. The average haemoglobin in both groups are equal, and the dose of exogenous epoetin is lower in patients treated with PD, but the difference is insignificant. Patients treated with PD are younger and with shorter duration of RRT, the difference is significant.

M. Chandra et al. (2) evaluate a group of 35 patients with ESRD, treated with HD and 35 patients on PD. Compared to HD, patients on PD have a significantly higher serum erythropoietin (CAPD $46,1 \pm 13,4$ vs. HD $16,9 \pm 2,2$ mU/ml) and hematocrite. Significant fluctuations of the levels of serum erythropoietin are present in patients on both HD and PD. There is a weak correlation between serum erythropoietin and hematocrite in both groups. They explain that with better biochemical milieu for red blood cell production, provided by PD, compared to HD.

By citing other studies, Manju Chandra et al. (2) accept that improvement of anemia in CAPD patients has been related to improved erythropoiesis, which in turn could result from increased red blood cell production, more efficient clearance of substances, that may nonspecifically inhibit erythropoiesis and improved protein metabolism.

K. Morris and M. Coulthard (17) accept that patients on continuous ambulatory peritoneal dialysis (CAPD) maintain higher haemoglobin concentrations than patients on intermittent peritoneal dialysis or on hemodialysis.

Very interesting is the suggestion, that patients with CKD maintain persistent Epo synthesis despite declining renal function, and this maintenance may result in part from increased liver Epo synthesis (4).

V. CONCLUSION

Our results and the results of other authors give reason to accept that interpretation of serum erythropoietin levels in the context of renal insufficiency remains controversial. An important reason for that is the lack of a measurable parameter for inadequate erythropoietin synthesis. Patients with renal failure may have normal erythropoietin levels although low for their degree of anemia, a condition addressed as „relative erythropoietin deficiency“ (Thomas Fehr...). Further prospective studies have to reveal whether measurement of erythropoietin may be predictive for the response to exogenous erythropoietin.

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