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ORIGINAL ARTICLE

Soluble Anti-erythropoietin Level as a Predictor of Erythropoietin Resistance in Patients Under Regular Hemodialysis

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Abstract

Background: **Anemia is multifactorial in ESRD cases. It has been shown to be primarily caused by insufficient erythropoietin (EPO) synthesis combined with erythropoietin resistance and an increased erythropoietin demand. EPO stimulates the production of red blood cells in the bone marrow. Therefore, recombinant human EPO therapy (rHuEPO) is the primary medication for ESRD-associated anemia.**

Objective: **Determine the predictive value of anti-EPO levels in the monitoring of erythropoietin resistance in those receiving hemodialysis.**

Patients and methods: **This Cross-Sectional Study was conducted in the hemodialysis facilities of the Department of Internal Medicine at Al-Azhar University Hospital for Boys in Cairo. During a six-month period, ninety subjects underwent regular hemodialysis. Patients were separated into two categories; the first group received rhuEPO therapy, while the second group did not.**

Results: **There was a statistically significant difference among our research population and the laboratory parameters anti-Erythropoietin antibodies, HB, HCT and EPO.IU (week). There was no statistically significant difference among the sexes and Co-morbidities in our research population.**

Conclusion: **Anti-EPO antibodies are generally prevalent among people on dialysis receiving rhuEPO. Resistance to rhuEPO medication can increase the risk of subsequent adverse outcomes in CKD cases. There were negative correlations among anti-EPO titre and laboratory data of CKD cases, including HB, HCT and MCHC, as well as the dose of rHuEPO administered.**

Keywords: Erythropoietin resistance, Hemodialysis, Soluble anti-erythropoietin

1. Introduction

Anemia is regarded as the most prevalent complication among cases with end-stage renal disease (ESRD), particularly those on maintenance dialysis. In addition, it has been identified as an independent risk factor and predictor of increased hospitalizations, failure to thrive, and significant cardiovascular events, such as heart failure and atherosclerosis.[1]

Anemia is multifactorial in ESRD cases. It has been shown to be primarily caused by insufficient erythropoietin (EPO) synthesis combined with erythropoietin resistance and an increased erythropoietin demand.[2] EPO stimulates the synthesis of red blood cells in the bone marrow. Therefore, recombinant human EPO therapy (rHuEPO) is the primary medication for ESRD-associated anemia.[3]

rHuEPO is a glycoprotein that is the biological equivalent of the endogenous compound used to treat anemia in cases with end-stage renal disease. There have been reports of resistance to rHuEPO, with cases requiring ever-increasing doses to maintain an adequate hemoglobin level. Antibody levels to EPO in the serum are a risk factor for EPO resistance.[4]

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After four weeks, the response to recombinant EPO therapy is evaluated by measuring hemoglobin and reticulocyte count. The optimal response to therapy is defined as an increase in hemoglobin level greater than 1 g/dl or a change in absolute reticulocyte count greater than 40 109 cells/l.[5]

It is observed that CKD cases receiving EPO therapy develop a condition known as EPO resistance, which is characterized by persistent anemia (hemoglobin less than 10–12 g/dl) or the need for extremely large doses of rHuEPO (300 IU/kg/week by subcutaneous route or 450 IU/kg/week intravenously).[1]

2. Patients and methods

This cross-sectional survey was conducted at the hemodialysis units of the Department of Internal Medicine at Al-Azhar University Hospital for Boys in Cairo. During a six-month period, ninety subjects underwent regular hemodialysis.

2.1. Inclusion criteria

Cases with at least 6 months of hemodialysis medication and an age among 18 and 60 years.

2.2. Exclusion criteria

Cases who do not meet the previous inclusion criteria, cases with active hemorrhage, active infection, or who are being treated for cancer, patients with anemia requiring a blood transfusion within one month prior to enrollment and cases with iron-deficiency anemia And expectant women.

Subjects were recruited and divided into 2 categories based on the inclusion and exclusion criteria: Group A consisted of 45 cases who were treated with rhEPO for at least 6 months. Group B consisted of 45 cases who did not receive rhEPO medication.

2.2.1. Procedures applied in the study

Cases were subjected to a comprehensive history (demographic information and medical history) and clinical evaluation.

2.3. Statistical methods

Continuous variable descriptive results were expressed as mean ± standard deviation. A paired t-test was utilized to compare quantitative variables. Using linear regression, the association among the antibodies and various clinical and laboratory parameters was investigated. All statistical analyses were conducted using the SPSS 22.0 program. *P* values less than 0.05 are considered significant.

3. Results

Tables 1–6, Figs. 1–5.

Table 1. The demographic parameters of the research groups.

	Group A (on EPO therapy) No. = 45	Group B (not on EPO therapy) No. = 45	Test value	*P* value	Sig.
Age (years)					
Mean ± SD	47.69 ± 10.49	54.91 ± 6.58	−3.914[b]	0.000	HS
Range	27–60	33–60			
Sex					
Female	25 (55.6%)	20 (44.4%)	1.111[a]	0.292	NS
Male	20 (44.4%)	25 (55.6%)			

P value > 0.05: Nonsignificant (NS); *P* value < 0.05: Significant (S); *P* value < 0.01: highly significant (HS).
[a] Chi-square test.
[b] Independent *t*-test.

Table 2. Comorbidities of the research groups.

	Group A No. (%)	Group B No. (%)	Test value[a]	*P* value	Sig.
HTN					
No	3 (6.7%)	10 (22.7%)	4.601	0.032	S
Yes	42 (93.3%)	34 (77.3%)			
DM					
No	36 (80.0%)	40 (88.9%)	1.353	0.245	NS
Yes	9 (20.0%)	5 (11.1%)			
Co-morbidities					

(*continued on next page*)

Table 2. (continued)

	Group A No. (%)	Group B No. (%)	Test value[a]	*P* value	Sig.
No	31 (68.9%)	29 (64.4%)	0.200	0.655	NS
Yes	14 (31.1%)	16 (35.6%)			
None	31 (68.9%)	29 (64.4%)			
IHD	8 (17.8%)	7 (15.6%			
Tertiary hyperparathyroidism	4 (8.9%)	2 (4.4%)			
HCV	1 (2.2%)	1 (2.2%)			
Polycystic kidney	1 (2.2%)	0 (0.0%)			
Bronchial asthma	0 (0.0%)	1 (2.2%)	7.800	0.648	NS
Below knee amputation of lt limb	0 (0.0%)	1 (2.2%)			
Epilepsy	0 (0.0%)	1 (2.2%)			
Rheumatoid arthritis	0 (0.0%)	1 (2.2%)			
Rheumatic heart	0 (0.0%)	1 ((2.2%)			
AF	0 (0.0%)	1 (2.2%)			
Family history					
No	40 (88.9%)	42 (93.3%)	0.549	0.459	NS
Yes	5 (11.1%)	3 (6.7%)			

P value > 0.05: Nonsignificant (NS); *P* value < 0.05: Significant (S); *P* value < 0.01: highly significant (HS).
[a] Chi-square test.

Table 3. Results of anti-Erythropoietin antibodies of the research groups.

	Group A (on EPO therapy) Anti −EPO AB Positive	Group B (not on EPO therapy) Anti −EPO AB Negative	Test value[a]	*P* value	Sig.
	No. = 45	No. = 45			
Mean (IQR)	44.35 (30.87–59.13)	5.16 (3.65–9)	−8.171	0.000	HS
Range	19.59–175.38	1.84–16			
Negative (less than 17)	0 (0.0%)	45 (100.0%)			
Low titre (17–50)	25 (55.6%)	undetectable	90.000	0.000	HS
Medium titre (51–100)	15 (33.3%)	undetectable			
High titre (more than 100	5 (11.1%)	undetectable			

P-value >0.05: Nonsignificant (NS); *P*-value <0.05: Significant (S); *P*-value< 0.01: highly significant (HS).
[a] Mann Whitney test.

Table 4. The laboratory parameters of the research groups.

	Group A	Group B	Test value	*P* value	Sig.
	No. = 45	No. = 45			
HB (gm/dl)					
Mean ± SD	9.35 ± 0.80	12.30 ± 0.52	−20.782[a]	0.000	HS
Range	7.4–10.9	11.1–13.2			
HCT (%)					
Mean ± SD	28.76 ± 300	37.70 ± 1.05	−18.818[a]	0.000	HS
Range	22–34.9	35.5–39.2			
MCV (fl)					
Mean ± SD	84.65 ± 5.52	86.50 ± 4.72	−1.708[a]	0.091	NS
Range	74–103	75.6–94			
MCH (pg)					
Mean ± SD	28.12 ± 2.23	28.49 ± 2.06	−0.815[a]	0.417	NS
Range	23–34	24–32			

(*continued on next page*)

Table 4. (continued)

	Group A	Group B	Test value	*P* value	Sig.
	No. = 45	No. = 45			
MCHC (gm/dl)					
Mean ± SD	31.83 ± 2.06	32.75 ± 2.14	−2.077[a]	0.041	S
Range	27–36	27–37			
RDW (%)					
Mean ± SD	14.53 ± 0.91	14.70 ± 0.65	−1.063[a]	0.291	NS
Range	12.4–18.1	13.2–15.9			
WBC (thousands/cmm)					
Mean ± SD	8.22 ± 1.49	7.99 ± 1.69	0.661[a]	0.510	NS
Range	5–10.5	4.8–10.7			
PLT (thousands/cmm)					
Mean ± SD	198.96 ± 38.09	195.78 ± 57.49	0.309[a]	0.758	NS
Range	110–286	117–346			
Reticulocyte count (%)					
Median (IQR)	0.31 (0.28–0.35)	1.21 (1.08–1.33)	−8.162[b]	0.000	HS
Range	0.12–0.53	0.51–1.6			
Creatinine (mg/dl)					
Mean ± SD	9.68 ± 2.33	9.38 ± 2.07	0.645[a]	0.521	NS
Range	4.5–16.9	4.6–14.9			
Urea (mg/dl)					
Mean ± SD	147.67 ± 38.80	133.18 ± 34.65	1.868[a]	0.065	NS
Range	73–287	70–218			
Uric acid (mg/dl)					
Mean ± SD	5.82 ± 0.97	5.99 ± 0.89	−0.882[a]	0.380	NS
Range	2.8–7.5	4.2–7.9			
PTH (pg/ml)					
Median (IQR)	261 (182–337)	202 (92–292)	−1.307[b]	0.191	NS
Range	28.4–1267	25–1458			
Iron (ug/dl)					
Mean ± SD	70.91 ± 22.44	70.13 ± 20.98	0.170[a]	0.866	NS
Range	28–105	30–112			
TIBC (ug/dl)					
Mean ± SD	248.53 ± 37.29	235.02 ± 32.23	1.839[a]	0.069	NS
Range	176–338	185–324			
T-SAT (%)					
Mean ± SD	27.89 ± 7.07	29.71 ± 9.21	−1.053[a]	0.295	NS
Range	12–40	13–46			
Ferritin (ng/ml)					
Median (IQR)	272 (128–354)	208 (104–321)	−1.227[b]	0.220	NS
Range	17–2849	6.5–841			
K (mmol/l)					
Mean ± SD	5.48 ± 0.64	5.37 ± 0.61	0.859[a]	0.392	NS
Range	3.9–6.6	4.3–6.6			
Na (mmol/l)					
Mean ± SD	137.09 ± 4.46	136.16 ± 4.33	1.007[a]	0.317	NS
Range	128–144	128–144			
Ca (mg/dl)					
Mean ± SD	8.96 ± 0.60	9.22 ± 0.63	−1.972[a]	0.052	NS
Range	7.7–10	6.8–10.2			
P (mg/dl)					
Mean ± SD	5.32 ± 0.67	5.23 ± 0.83	0.558[a]	0.578	NS
Range	3.7–7.2	3.6–7.3			

P-value >0.05: Nonsignificant (NS); *P*-value <0.05: Significant (S); *P*-value< 0.01: highly significant (HS).

[a] Independent *t*-test.

[b] Mann Whitney test.

Table 5. Correlation among Anti- Erythropoietin antibodies with a variety of factors being investigated.

	Erythropoietin antibodies			
	Group A		Group B	
	R	*P* value	*r*	*P* value
HB (gm/dl)	**−0.709****	**0.000**	0.118	0.440
HCT (%)	**−0.462****	**0.001**	0.063	0.682
MCV (fl)	0.195	0.200	0.110	0.473
MCH (pg)	0.218	0.150	0.117	0.443
MCHC (gm/dl)	0.145	0.341	0.008	0.958
RDW (%)	0.071	0.643	0.194	0.202
WBC (thousands/cmm)	−0.262	0.082	0.035	0.820
PLT (thousands/cmm)	0.170	0.264	**0.386****	**0.009**
Reticulocyte count (%)	0.026	0.866	0.092	0.548
Creatinine (mg/dl)	0.035	0.821	**0.394****	**0.007**
Urea (mg/dl)	0.260	0.085	0.083	0.588
Uric acid (mg/dl)	0.183	0.230	−0.058	0.706
PTH (pg/ml)	**0.641****	**0.000**	**0.535****	**0.000**
Iron (ug/dl)	0.011	0.945	**0.325***	**0.029**
TIBC (ug/dl)	0.063	0.679	−0.005	0.974
T-SAT (%)	0.001	0.996	0.255	0.090
Ferritin (ng/ml)	−0.036	0.812	0.247	0.102
K (mmol/L)	0.007	0.965	0.143	0.349
Na (mmol/L)	0.006	0.968	−0.020	0.897
Ca (mg/dl)	0.220	0.146	0.233	0.123
P (mg/dl)	−0.013	0.932	−0.162	0.288
Dose of EPO.IU (week)	**0.728****	**0.000**	–	–

Table 6. Relation among Anti-Erythropoietin antibodies titre grades of Group A with different studied variables.

	Low titre	Medium titre	High titre	Test value	*P* value	Sig.
	No. = 25	No. = 15	No. = 5			
HB (gm/dl)						
Mean ± SD	9.85 ± 0.46	8.87 ± 0.53	8.22 ± 0.90	27.587[a]	0.000	HS
Range	9–10.9	7.6–9.7	7.4–9.6			
HCT (%)						
Mean ± SD	30.03 ± 1.76	27.62 ± 3.39	25.80 ± 3.85	7.365[a]	0.002	HS
Range	27.6–34	23.1–34.9	22–30			
MCV (fl)						
Mean ± SD	84.06 ± 4.54	85.23 ± 6.74	85.88 ± 6.88	0.336[a]	0.716	NS
Range	74–91	74–103	74–91			
MCH (pg)						
Mean ± SD	27.71 ± 2.20	28.48 ± 2.46	29.14 ± 1.26	1.154[a]	0.325	NS
Range	23–31	23–34	27–30			
MCHC (gm/dl)						
Mean ± SD	31.66 ± 2.16	32.05 ± 1.97	32.08 ± 2.20	0.201[a]	0.819	NS
Range	27–36	28–35	29–35			
RDW (%)						
Mean ± SD	14.64 ± 0.94	14.19 ± 0.73	14.96 ± 1.13	1.824[a]	0.174	NS
Range	13.7–18.1	12.4–15.4	13.6–16.4			
WBC (thousands/cmm)						
Mean ± SD	8.46 ± 1.40	8.23 ± 1.57	6.94 ± 1.32	2.291[a]	0.114	NS
Range	5.7–10.5	5.8–10.5	5–8.6			
PLT (thousands/cmm)						
Mean ± SD	189.24 ± 34.39	207.20 ± 42.21	222.80 ± 32.80	2.267[a]	0.116	NS
Range	110–268	143–286	174–265			
Reticulocyte count (%)						
Median (IQR)	0.31 (0.28–0.35)	0.31 (0.27–0.42)	0.31(0.31–0.33)	0.504[b]	0.777	NS
Range	0.12–0.51	0.14–0.53	0.26–0.47			
Creatinine (mg/dl)						
Mean ± SD	9.55 ± 2.65	9.80±± 2.14	9.94 ± 1.23	0.087[a]	0.917	NS
Range	4.5–16.9	6–13.1	8.8–11.5			
Urea (mg/dl)						
Mean ± SD	141.00 ± 28.51	150.60 ± 52.56	172.20 ± 30.95	1.439[a]	0.249	NS
Range	99–198	73–287	144–220			

(*continued on next page*)

Table 6. (continued)

	Low titre	Medium titre	High titre	Test value	*P* value	Sig.
	No. = 25	No. = 15	No. = 5			
Uric acid (mg/dl)						
Mean ± SD	5.69 ± 0.84	5.91 ± 1.18	6.16 ± 1.02	0.572[a]	0.569	NS
Range	3.9–7.1	2.8–7.4	5–7.5			
PTH (pg/ml)						
Median (IQR)	218 (62–284)	310(187–352)	739 (464–1123)	18.006[b]	0.000	HS
Range	28.4–372	145–427	463–1267			
Iron (ug/dl)						
Mean ± SD	72.08 ± 22.29	71.73 ± 22.27	62.60 ± 26.93	0.376[a]	0.689	NS
Range	31–104	28–105	30–104			
TIBC (ug/dl)						
Mean ± SD	248.84 ± 37.24	249.07 ± 38.11	245.40 ± 43.39	0.019[a]	0.981	NS
Range	196–338	176–327	208–297			
T-SAT (%)						
Mean ± SD	28.36 ± 7.01	28.13 ± 6.93	24.80 ± 8.58	0.530[a]	0.592	NS
Range	14–37	12–40	14–35			
Ferritin (ng/ml)						
Median (IQR)	281 (219–354)	265 (148–346)	94 (76–354)	0.893[b]	0.640	NS
Range	24–2849	17–627	17–419			
K (mmol/l)						
Mean ± SD	5.42 ± 0.53	5.63 ± 0.77	5.32 ± 0.75	0.690[a]	0.507	NS
Range	4.7–6.6	3.9–6.6	4.4–6.4			
Na (mmol/l)						
Mean ± SD	136.92 ± 5.01	137.20 ± 3.88	137.60 ± 3.91	0.053[a]	0.948	NS
Range	128–144	129–143	134–144			
Ca (mg/dl)						
Mean ± SD	8.86 ± 0.54	9.05 ± 0.62	9.22 ± 0.88	0.985[a]	0.382	NS
Range	7.9–10	7.7–9.9	8–10			
P (mg/dl)						
Mean ± SD	5.37 ± 0.59	5.20 ± 0.87	5.40 ± 0.38	0.331[a]	0.720	NS
Range	3.7–6.3	4.1–7.2	4.8–5.8			
Dose of EPO.IU (week)						
Mean ± SD	4480 ± 1758.79	6933.33 ± 1830.95	11200 ± 1788.85	32.280[a]	0.000	HS
Range	4000–12000	4000–8000	8000–12000			

P value > 0.05: Nonsignificant (NS); *P* value < 0.05: Significant (S); *P* value < 0.01: highly significant (HS).

[a] One Way ANOVA test.

[b] Kruskal Wallis test.

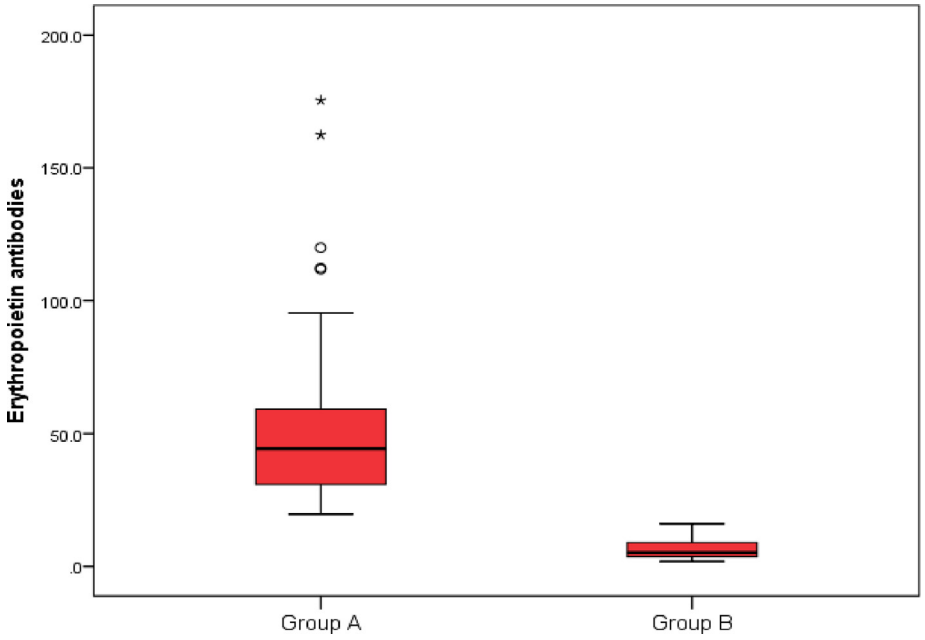

Fig. 1. Box plot for the level of anti-erythropoietin antibodies in Group A and Group B cases.

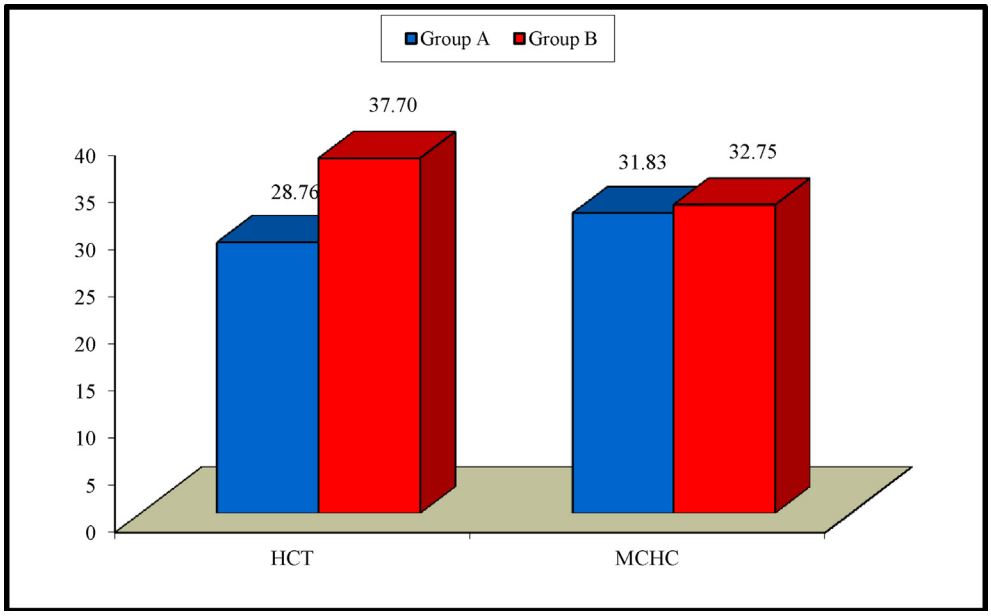

Fig. 2. Bar chart for hematocrit & MCHC in Group A & Group B cases.

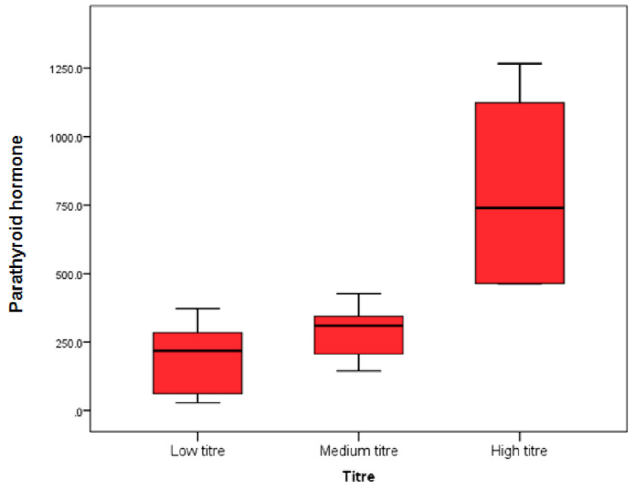

Fig. 3. Relation among Anti-Erythropoietin antibodies titre grades of Group A & parathyroid hormone.

4. Discussion

In cases with chronic kidney disease (CKD), anemia is a common and serious condition that can have devastating consequences. The problem gets worse as kidney disease advances. A reduced quality of life and an increased risk of death are two of anemia in CKD's negative impacts. Anemia is a major predictor of cardiovascular events in CKD cases and has been linked to an increased risk of hospitalization, a longer length of time in the hospital, a lower quality of life and a higher risk of death and disease due to the condition. Anemia is a common risk factor for CKD, although it can be avoided with the right measures.[6]

Some participants in the current research also suffered from co-morbidities such as high blood pressure, diabetes, ischemic heart disease and secondary hyperparathyroidism. With the exception of hypertension, no significant difference was found among the groups statistically ($P > 0.05$). Hypertension was more common in group B (22.7% vs. 6.7% overall) than in group A. This distinction was statistically significant ($P < 0.05$).

Noshad's view is supported by this result. A prospective study of 80 cases with ESRD (40 on hemodialysis and 40 on predialysis) found that post injection of erythropoietin, systolic, diastolic & mean arterial blood pressure values increased significantly in the hemodialysis group, and the increases were significantly greater than in nonhemodialysis CKD.

In addition, **Ohki *et al.***[7] found that more than half of the 36 nondialysis CKD cases with renal anemia who were treated with an Erythropoietin-stimulating drug for 24 weeks required an increase in the antihypertensive medicine provided.

The following was discovered by analyzing the hematological differences among the two groups in the current research: When comparing groups A and B, the lower hematological indicators in group A were highly statistically significant. There was a significant difference among 2 groups with respect to reticulocyte count (0.31 vs 1.21%, P 0.05), HB (9.35 ± 0.80 vs 12.30 ± 0.52 gm/dl) and HCT (28.76 ± 3.00 vs 37.70 ± 1.05%, $P < 0.05$).Since this population was receiving rhuEPO to address their anemia, the results made sense. These results further imply that the existence of Anti-Erythropoietin

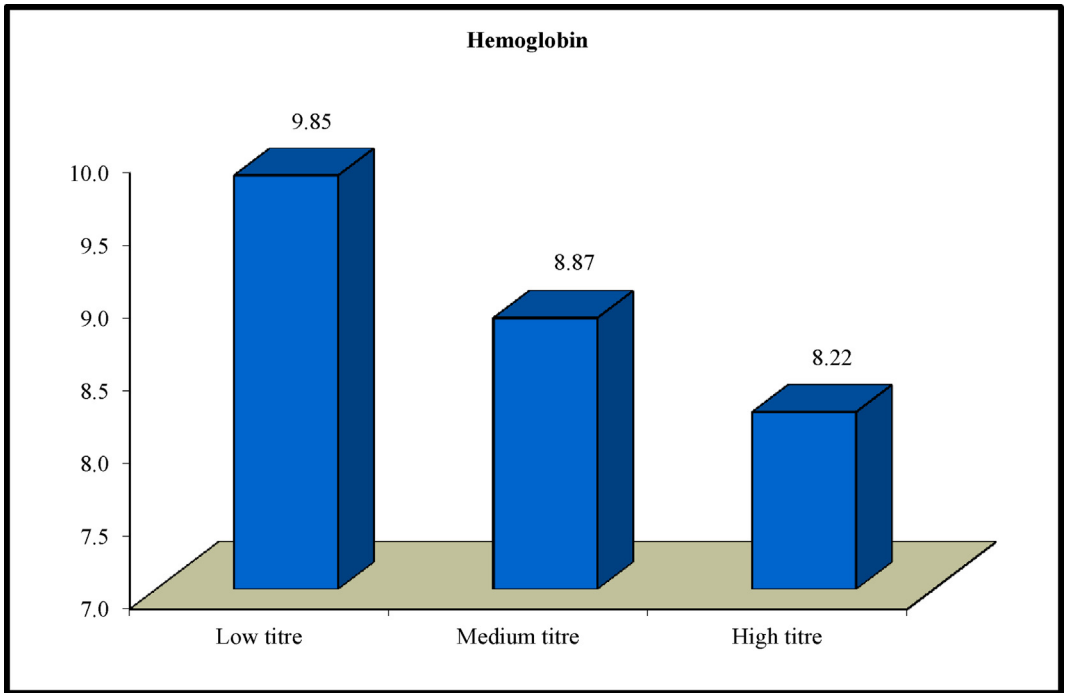

Fig. 4. Relation among Anti-Erythropoietin antibodies titre grades of Group A & Hemoglobin.

Antibodies impeded RBC formation in the bone marrow of individuals receiving rhuEPO therapy. Cases with strong anti-EPO antibodies are more likely to have a poor response and inefficient erythropoiesis, as seen by their low reticulocyte count.

These results are consistent with those found by **Sarhan** et al.,[8] who found that anti-EPO antibody was positively correlated with EPO doses (r = 0.309, *P* value = 0.011), iron doses (r = 0.266, *P* value = 0.003), and erythropoietin resistance index (r = 0.417, *P* value = 0.0001) but negatively correlated with hemoglobin (r = −0.661, *P* value = 0.0001). In contrast to the present data, a negative connection was found with PTH (r = −0.259, *P* value = 0.014).

On the other hand, anti-EPO antibodies were found to have no significant relationship with

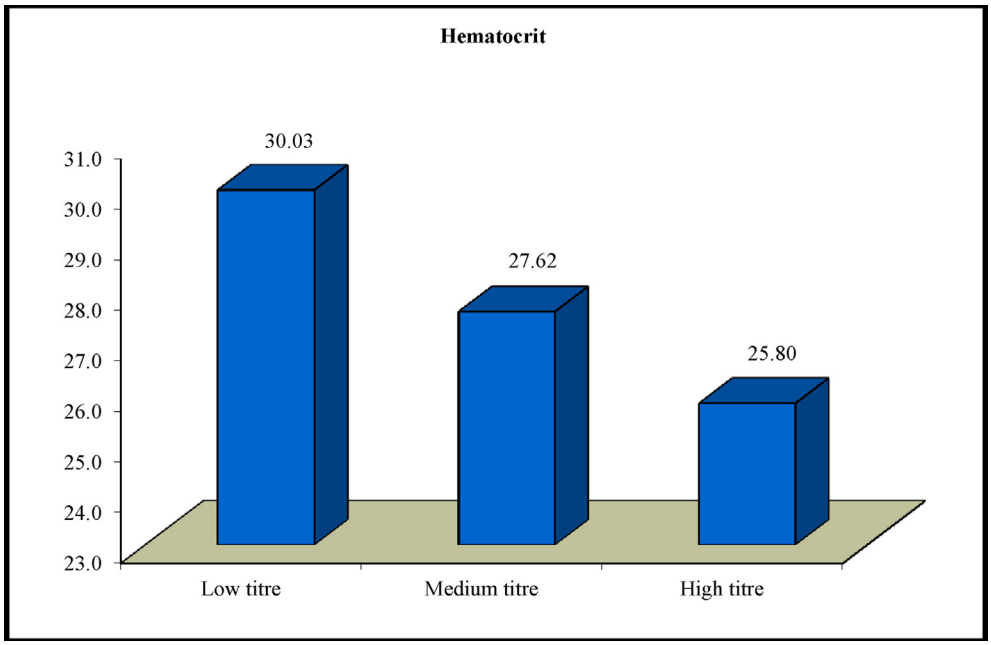

Fig. 5. Relation among Anti-Erythropoietin antibodies titre grades of Group A & Hematocrit.

hemoglobin, hemoglobin concentration, urea, creatinine, serum iron, ferritin, T-SAT percent, or reticulocyte by **Zafar** et al.[1] These antibodies may not be able to neutralize anything.

Research by **Rahbar** et al.[9] on 128 dialysis cases with refractory anemia who were treated with erythropoietin reveals that 45 cases (or 36%) had anemia with hemoglobin levels below 10 mg/dL. Serum antibodies against erythropoietin were present in only 3 cases with pure red cell aplasia.

Mean anti-Erythropoietin antibodies were significantly higher in group A (on EPO therapy) than in group B (not on EPO therapy) in the current investigation (44.35 mU/ml vs. 5.16 mU/ml, respectively; *P* value 0.001). Group A cases in the current research were stratified into three groups: those with a low titre of anti-EPO antibody (17 mU/ml), a medium titre (51–100 mU/ml), and a high titre of anti-EPO antibody (>100 mU/ml). Five-sixths (54.6%), one-third (33.3%), and eleven percent (11.1%) of cases in group A had them.

This stratification proved to be a useful Comparison tool among 3 groups and revealed that the high the antibody titre the low the Hb (8.22 ± 0.90 vs. 8.87 ± 0.53 vs. 9.85 ± 0.46 gm/dl, respectively) and the HCT (25.80 ± 3.85 vs. 27.62 ± 3.39 vs. 30.03 ± 1.76%, respectively). In group A, high antibody titre was favorably linked with serum PTH (739 vs. 310 vs. 218 pg/ml). Group A cases had a significantly higher rate of anti-EPO antibody elevation compared to the other two groups (11200 ± 1788.85 IU vs. 6933.33 ± 1830.95 IU vs. 4480 ± 1758.79 IU, respectively; $P < 0.001$).

Acquired PRCA due to recombinant erythropoietin (rHuEPO) was investigated by **Padhi *et al.***[10] The patients in his study had serum antibody against EPO levels that were above the diagnostic threshold of 53.20 mIU/mL. A resistance to EPO at this dose is indicated. Both exogenous and endogenous erythropoietin-stimulating drugs were neutralized by these antibodies.

Cases with chronic kidney disease who are undergoing hemodialysis are likely to have anti-EPO antibodies, as was shown in a recent study by **Khalid.**[11] which analyzed the presence of Anti-EPO antibodies in 150 CKD patients. The prevalence of anti-erythropoietin antibody was also determined by **Sarhan** et al.[8] in their analysis of 90 hemodialysis cases; they found that 45.6% of them (41 cases) had this antibody. In addition, 51 cases were positive for anti-EPO antibodies and 35 cases were negative for anti-EPO antibodies in a study of 86 cases undergoing routine hemodialysis by **Zafar** et al.[1]

4.1. Conclusions

Members on hemodialysis who are given rhuEPO frequently develop anti-EPO antibodies. There were negative associations among anti-EPO titre and laboratory data of people with chronic kidney disease (CKD), including Hb, HCT, and MCHC, suggesting that resistance to rhuEPO treatment may enhance the future risk of unfavorable outcomes in individuals with CKD.

Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

The authors have no financial interest to declare in relation to the content of this article.

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