Effect of recombinant human erythropoietin treatment on left ventricular hypertrophy and cardiac function in dialysis patients

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Background
Cardiovascular disease is a significant complication in chronic kidney disease and a major cause of death in dialysis patients. Anemia is associated with reduced survival in patients with renal disease, and anemia is independently associated with an increased risk of cardiovascular disease. The body adapts to anemia by increasing cardiac output, which may result in cardiac remodeling and progression of left ventricular (LV) growth.
Aim
The aim of this study was to shed light on the effects of correction of anemia after therapy with recombinant human erythropoietin (rHuEPO) on left ventricular hypertrophy (LVH) and consequently LV function in dialysis patients. So we studied 40 hemodialysis patients with hemoglobin (Hb) less than 10 g/dl as well as 10 age-matched and sex-matched hemodialysis patients with Hb more than 11 g/dl who never received erythropoietin as a control group.
Patients and methods
All participants of the study were subjected to full medical history, thorough medical examination, and investigations including complete blood count, serum ferritin, and echocardiography.
Results
A significant increase in Hb, packed cell volume (PCV%), and red blood cells (RBCs) count was seen at all months of the study period, with mean Hb at the start of the study being 7.96±0.72 g/dl and at the end of treatment being 10.67±0.83 g/dl. There is a significant increase in ejection fraction (EF%) with significant reduction in left ventricular mass index (LVMI) after treatment in comparison with pretreatment, which means improvement of cardiac function and reduction of LVH after treatment with rHuEPO.
Conclusion
This prospective study showed that correction of anemia with rHuEPO in the patients undergoing hemodialysis with Hb level less than 10 g/dl led to correction of LVH, with improvement of the cardiac function.

Keywords:
anemia, chronic kidney disease, erythropoietin, left ventricular hypertrophy

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Introduction

Chronic kidney disease (CKD) is a growing public health epidemic that is associated with markedly increased risk of cardiovascular disease (CVD) and mortality [1].

The prevalence of CVD is increased among patients in all stages of CKD. The Cardiovascular Health Study analysis demonstrated that per every 10 ml/min/1.73 m^2 decrease in glomerular filtration rate, the risk of CVD and all-cause mortality increased by 5 and 6%, respectively. In end-stage renal failure, the CVD is by far the leading cause of morbidity and mortality causing 40–50% of hospitalizations and deaths [2].

There is a high prevalence of left ventricular hypertrophy (LVH) in CKD. In fact, LVH is present in more than 70% of patients commencing dialysis (Dharawat *et al.*, 2009) [3].

Anemia is a severe complication of CKD that is seen in more than 80% of patients with impaired renal function [3]. Although there are many mechanisms involved in the pathogenesis of renal anemia, the primary cause is inadequate production of erythropoietin (EPO) by the damaged kidneys. EPO is produced in the peritubular cells of the kidney and is the major hormone involved in the synthesis of red blood cells (EPO). When EPO levels are low, an inadequate number of oxygen-

carrying red blood cells are produced. Anemia decreases oxygen supply all over the body and causes decreased exercise capacity, cognitive impairment, and diminished quality of life [3].

Anemia has also been implicated in the development of congestive heart failure and LVH [4]. Although treatment with recombinant EPO has improved the management of anemia in CKD, anemia persists as a significant problem in the disease [5].

The aim of this study was to shed light on the effects of correction of anemia after therapy with recombinant human erythropoietin (rHuEPO) on LVH and consequently left ventricular (LV) function in dialysis patients as regarding assessment of systolic function and LV measurements.

Patients and methods

This cohort prospective study was conducted on 40 hemodialysis patients with hemoglobin (Hb) less than 10 g/dl as case group and 10 age-matched and sex-matched hemodialysis patients with Hb more than 11 g/dl who never received EPO as a control group.

All participants of this study were submitted to full medical history with focus on manifestations of CKD, manifestations of heart failure, manifestations of anemia, and cause of renal failure, either diabetes mellite (DM), hypertension (HTN), or any other cause.

Medical examination focused on signs of CKD, signs of heart failure, and signs of anemia. Complete blood count and serum ferritin were measured.

For all participants, a baseline investigation was done before treatment, including complete blood picture with focusing on red blood cells (RBCs) count, packed cell volume (PCV%), serum ferritin, and echocardiography.

Echocardiography was done for all participants at the start of the study. Complete blood count was done monthly for 6 months. At the end of the study, complete blood count and echocardiography were again done for all participants.

Statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program statistical package for the social sciences (SPSS) version 20 (Oracle Corporation, Chicago, United States).

Descriptive data

Descriptive statistics were calculated for the data in the following form:

(1) Mean and SD for quantitative data.
(2) Frequency and distribution for qualitative data.

Analytical statistics

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:

(1) Student's *t*-test used to compare means of two groups of quantitative data.
(2) Paired *t*-test used to compare mean of variables in different time periods of quantitative data.
(3) Intergroup comparison of categorical data was performed by using Fisher exact test.

P value less than 0.05 was considered statistically significant, whereas more than 0.05 was considered statistically insignificant.

Results

The age of the studied group ranges from 18 to 70 years, with mean age of 52.2±12.44 years. Overall, 48% were males and 52% were females. The weight of the studied group ranges from 54 to 110 kg, with mean weight of 77.44±15.18 kg; height ranges from 150 to 190 cm, with mean height of 169.4±7.79 cm; and BMI ranges from 19 to 35.75 kg/m^2, with mean BMI of 26.92±4.29 kg/m^2 (Table 1). This study shows nonsignificant difference between case and control regarding age, sex, weight, height, BMI, HTN, and DM (Table 2).

There is a significant increase in Hb level, PCV%, and RBCs count at all months of the study period (Tables 3–5), and there is also a significant reduction in Hb, PCV%, and RBCs count in cases in comparison with control in all months of the study (Tables 6–8).

Table 1 Distribution of the studied group

All the studied group (50)	Mean±SD	Range
Age (years)	52.2±12.44	18–70
Sex [*n* (%)]		
Male	21	42.0
Female	29	58.0
Weight (kg)	77.44±15.18	54–110
Height (cm)	169.4±7.79	150–190
BMI (kg/m^2)	26.92±4.29	19.0–35.75

Table 2 Comparison between case and control regarding age, sex, weight, height, and BMI

	Case group (40) (mean ±SD)	Control group (10) (mean±SD)	*t*-Test	*P* value
Age (years)	52.1±12.73	52.6±11.86	0.11	0.91 (NS)
Sex [*n* (%)]				
Male	16 (40.0)	5 (50.0)	0.11	0.082 (NS)
Female	24 (60.0)	5 (50.0)		
Weight (kg)	76.05±16.33	83.0±7.57	1.3	0.20 (NS)
Height (cm)	169.0±8.51	171.0±3.59	0.72	0.47 (NS)
BMI (kg/m^2)	26.56±4.47	28.35±3.32	1.19	0.24 (NS)

Table 3 Hemoglobin difference at different follow-up periods from baseline among case group

Hemoglobin	First month	Second month	Third month	Fourth month	Fifth month	Sixth month	*P* value
Mean±SD (g/dl)	7.96 ±0.72	8.7±0.76	9.39 ±1.05	9.87±0.92	10.46 ±0.91	10.67 ±0.83	P_1=0.001 (S); P_2=0.001 (S); P_3=0.001 (S); P_4=0.001 (S); P_5=0.001 (S)

Table 4 PCV% difference at different follow-up periods from baseline among case group

PCV%	First month	Second month	Third month	Fourth month	Fifth month	Sixth month	*P* value
Mean±SD (cm^3)	24.13 ±2.41	25.66 ±2.51	27.5 ±3.74	28.47 ±3.38	30.26 ±3.22	31.41 ±2.32	P_1=0.001 (S); P_2=0.001 (S); P_3=0.001 (S); P_4=0.001 (S); P_5=0.001 (S)

PCV, packed cell volume.

Table 5 RBCs count difference at different follow-up periods from baseline among case group

RBCs (10^6/cmm)	First month	Second month	Third month	Fourth month	Fifth month	Sixth month	*P* value
Mean ±SD	2.80 ±0.34	2.93±0.24	3.05 ±0.31	3.11 ±0.34	3.48 ±0.56	3.53 ±0.44	P_1=0.046 (S); P_2=0.001 (S); P_3=0.001 (S); P_4=0.001 (S); P_5=0.001 (S)

RBCs, red blood cells; S, significant.

Table 6 Comparison between case and control group regarding hemoglobin level at different follow-up periods

Hemoglobin (g/dl)	Case group (40) (mean±SD) (g/dl)	Control group (10) (mean±SD) (g/dl)	*t*-Test	*P* value
First month	7.96±0.72	12.0±0.67	16.13	0.001 (S)
Second month	8.7±0.76	12.98±1.32	13.63	0.001 (S)
Third month	9.39±1.05	12.42±1.75	7.08	0.001 (S)
Fourth month	9.87±0.92	12.12±1.2	6.53	0.001 (S)
Fifth month	10.46±0.91	12.0±1.27	4.42	0.001 (S)
Sixth month	10.67±0.83	11.92±1.45	3.63	0.001 (S)

S, significant.

Table 7 Comparison between case and control group regarding PCV% at different follow-up periods

PCV%	Case group (40) (mean±SD (cm^3)	Control group (10) (mean±SD) (cm^3)	*t*-Test	*P* value
First month	24.13±2.41	35.16±2.01	13.32	0.001 (S)
Second month	25.66±2.51	37.6±3.44	12.46	0.001 (S)
Third month	27.5±3.74	36.9±4.72	6.74	0.001 (S)
Fourth month	28.47±3.38	35.14±4.35	5.27	0.001 (S)
Fifth month	30.26±3.22	34.32±5.86	2.98	0.005 (S)
Sixth month	31.41±2.32	35.92±5.0	4.24	0.001 (S)

PCV, packed cell volume.

A significant reduction in serum ferritin in cases in comparison with control is seen at the start of the study (Table 9).

There is a significant increase in EF% in cases after treatment in comparison with before treatment, and also a significant reduction is seen in left ventricular

end systolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), interventricular septal diameter (IVSD), posterior wall thickness diameter (PWtD), LVM, and left ventricular mass index (LVMI) in cases after treatment in comparison with before treatment. Significant increase is seen in LVESD, left atrial diameter (LAD), IVSD, PWtD, LVM, and LVMI in cases before treatment in comparison with control, a significant increase in LAD in cases after treatment in comparison with control, and also a significant reduction in ejection fraction (EF%) in cases before treatment in comparison with control (Table 10).

Discussion

Anemia in patients with CKD is associated with cardiovascular complications. Anemia has been independently associated with the development of LVH [6].

The use of erythropiotin (ESAs) in the management of renal anemia has been shown to improve survival, reduce cardiovascular morbidity, and enhance quality of life [7].

This study shows significant reduction in Hb, PCV%, and RBCs count in cases in comparison with control in all months of the study, and this indicates high prevalence of anemia in hemodialysis (HD) patients. This finding is consistent with the population-based study using National Health And Nutrition Examination Survey conducted in the USA that exhibited prevalence of anemia increases progressively as the estimated glomerular filtration rate decreases to less than 60 ml/min/1.73 m^2 [8].

Recently, large population-based studies about the prevalence of anemia in nondialysis CKD were reported. The recent National Health And Nutrition Examination Survey report showed that the prevalence

Table 8 Comparison between case and control group regarding RBCs count at different follow-up periods

RBCs	Case group (40) (mean±SD) (10^6/cm^2)	Control group(10) (mean±SD) (10^6/cm^2)	*t*-Test	*P* value
First month	2.80±0.34	4.18±0.46	10.77	0.001 (S)
Second month	2.93±0.24	4.08±0.10	14.82	0.001 (S)
Third month	3.05±0.31	4.22±0.29	10.93	0.001 (S)
Fourth month	3.11±0.34	4.34±0.39	9.98	0.001 (S)
Fifth month	3.48±0.56	4.1±0.54	4.1	0.05 (S)
Sixth month	3.48±0.44	4.18±0.61	4.19	0.001 (S)

RBCs, red blood cells; S, significant.

Table 9 Comparison between case and control group regarding ferritin level at start of the study

	Case group (40) (mean±SD)	Control group (10) (mean±SD)	*t*-Test	*P* value
Serum ferritin (ng/dl)	503.15±265.77	732.4±98.03	2.67	0.01 (S)

S, significant.

Table 10 Echocardiographic findings

	Case group before (40) (mean±SD)	Case group after (40) (mean±SD)	Control group (10) (mean±SD)	P_1 (before and control)	P_2 (after and control)	P_3 (before and after)
LVEDD (cm)	4.37±0.82	4.75±0.89	5.02±0.57	0.48 (NS)	0.41 (NS)	0.003 (S)
LVESD (cm)	3.78±0.85	3.33±1.05	3.08±0.20	0.014 (S)	0.99 (NS)	0.001 (S)
LAD (cm)	3.62±0.78	3.53±0.71	3.06±0.08	0.028 (S)	0.018 (S)	0.11 (NS)
EF%	62.11±8.9	65.03±8.3	68.98±2.83	0.022 (S)	0.15 (NS)	0.001 (S)
LVESD (cm)	1.38±0.21	1.17±0.15	1.18±0.13	0.006 (S)	0.82 (NS)	0.001 (S)
PWtd (cm)	1.40±0.20	1.17±0.12	1.14±0.08	0.001 (S)	0.44 (NS)	0.001 (S)
LVM (g)	297.4±76.3	213.2±56.55	203.4±37.56	0.001 (S)	0.65 (NS)	0.001 (S)
LVMI (g/m^2)	157.8±39.1	114.9±27.02	109.0±16.83	0.001 (S)	0.34 (NS)	0.001 (S)

EF, ejection fraction; LAD, left atrial diameter; LVEDD, left ventricular end systolic diameter; LVESD, left ventricular end systolic diameter; LVMI, left ventricular mass index; PWtD, posterior wall thickness diameter; S, significant.

of anemia was 15.4% in patients with CKD stages 1–5 compared with 7.5% in non-CKD population (Stauffer *et al.* 2014) [9]. A Chinese report showed that 51.5% of patients with CKD stages 1–5 had anemia (Li *et al.* 2016) [10].

This study also shows significant increase in Hb concentration, PCV%, and RBCs count at all follow-up periods of the study. The mean Hb at baseline in our study was 7.96±0.72 g/dl and the mean Hb at the end of the study was 10.67±0.83 g/dl. This means that all cases of the study responded well to treatment with rHuEPO and achieved the target Hb of 11–12 g/dl. These results were consistent with the study of Abdu *et al.* [11] which shows that all patients of the study responded well to treatment with rHuEPO, and all patients achieved the target Hb of 11 g/dl [11].

Moreover, these results are consistent with the results of a multicenter study by Dimković *et al.* [12], which showed that Hb was significantly increased by increasing the dose of EPO B during the study compared with the baseline values. This significant increase was recorded after the third month of therapy, and it continued up to the 12th month. Although at the end of the study, 52% of patients achieved the target Hb level, a higher percentage of patients (83%) achieved Hb levels more than 11 g/dl, which is in accordance with the current guidelines (10–12 g/dl) [12].

These results are consistent with the data from a study by Al-Shohaib *et al.* [13] which re-enforced the previous conclusion with Julphar's Epotin. Efficacy and tolerability to correct anemia and to maintain Hb within the target range of 11–12 g/dl in 80% of patients with ESKD on maintenance hemodialysis was achieved as per KDOQI Working Group on Anemia [14].

The target Hb in the present study was assigned to limit between 11 and 12 g/dl, and this is consistent with the study by Al-Shohaib *et al.* [13] which showed that this is the optimal target hemoglobin level in patients with ESRD who are under dialysis, and current guidelines recommended that Hb should not be increased more than 12 g/dl in high-risk patients with CVDs [13].

Finally, the KDOQI clinical practice recommendation clearly addressed that the Hb target should generally be in the range of 11–12 g/dl in dialysis and nondialysis patients with CKD receiving EPO stimulating agent therapy [15].

The echocardiographic findings in our study show a significant reduction in LVEDD and LVESD in cases after treatment in comparison with pretreatment and significant increase in LVESD and LAD in cases before treatment in comparison with control. These results are consistent with the study done by Wirginia Tomczak *et al.* [16], which shows a reduction in LV end-diastolic diameter, which also suggest a decrease in preload. These results are also consistent with a study done by Prasert and Siriwiwatanakul [17], which shows that there was a significant regression of LV end-diastolic diameter and LVMI especially in the highest tertile of basal LVMI.

Our results also show significant increase in EF% in cases after treatment in comparison with cases before treatment and significant reduction in EF% in cases before treatment in comparison with control, and this demonstrate that correction of anemia in hemodialysis patients by EPO resulted in significant improvement in LVEF. This is consistent with the study done by Hampl *et al.* [18] which showed that correction of anemia by rHuEPO resulted in significant improvement in NYHA class and LVEF, which is also consistent across high-risk subgroups [18].

In contrary to our results, data from the study by Tomczac-Watras *et al.* (2009) showed that the increase in Hb level did not significantly influence the EF% in the analyzed group of patients. Moreover, in contrary to our results, a study by Dimkovic *et al.* [12] showed that during their study, the LVEF values were not significantly changed, thus indicating the preserved LV function after the correction of hyperdynamic state, but this study had certain limitations. Its design was predominantly focused on the correction of anemia as an important risk factor for the development of LVH, whereas other risk factors were not investigated [12].

A significant reduction was seen in IVSD, PWtd, LVM, and LVMI in cases after treatment in comparison with before treatment, and this indicates an improvement in LVH in cases after correction of anemia by rHuEPO. These results are consistent with the study done by Ayus *et al.* [19] which showed that among patients with advanced chronic renal insufficiency, a reduction in Hb level is associated with increased odds of having echocardiographic LVH, and administration of EPO in patients with anemia with Hb less than 10 g/dl with severe renal

insufficiency reduced LVMI after 6 months of therapy [19].

Our results also are consistent with the study by Hampl *et al.* [18]. We were able to demonstrate that regression and prevention of LVH is possible. Even in the high-risk subgroup of HD patients, namely, those with CAD, diabetes mellitus, hypertension, or those with very low LVEF, regression of LVH was achieved [18].

In contrary to our study results, a prospective Canadian study reported that normalization of the Hb, after a 48-week trial of erythropoietin therapy, did not lead to echocardiographic evidence of regression of LVH or LV dilatation [20].

In contrary to our study results, data from a study by Roger *et al.* [21] showed that only 33% of anemic participants had LVH. The lower prevalence of LVH noted by Roger *et al.* [21] compared with ours may be owing to enrolment of younger patients with more preserved levels of renal function and higher Hb levels [21].

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Conflicts of interest
There are no conflicts of interest.

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