

Effect of Erythropoietin Therapy on the Lipid Profile in Patients with Chronic Kidney Disease – A Single Center Study

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Abstract

Dyslipidemia is common in chronic kidney disease patients and alterations in serum lipid profile vary widely depending on the level of kidney function. We studied two hundred Iraqi patients who were diagnosed as having chronic kidney disease from June 2011 to January 2013. They were given erythropoietin for seven months. One hundred sixty patients (80%) showed response to treatment with an improvement in lipid profile, while the other 40 patients (20%) showed no significant response to treatment. In conclusion, treatment with erythropoietin seems to positively influence the lipid profile in patients with chronic kidney disease.

Keywords: Chronic kidney disease; Epoetin; Lipids

Introduction

Patients with chronic kidney disease (CKD) are at higher risk of cardiovascular disease (CAD) than subjects in the general population [1-3]. Dyslipidemia is common in CKD patients and alterations in serum lipid profile vary widely depending on the level of kidney function and the degree of proteinuria [4-6]. Patients frequently have elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The classic lipid profile of late-stage CKD includes increased triglyceride (TG) levels, moderately elevated or normal LDL cholesterol levels and low high density lipoprotein cholesterol (HDL-C) levels [4,5,7].

The reduction in serum levels of HDL-C represents an important lipoprotein abnormality in patients with decreased renal function [5-9]. Low levels of HDL-C have also been shown to be an independent risk factor for CAD and premature atherosclerosis regardless of serum LDL-C and TG levels [10,11]. HDL-C is a potent anti atherogenic lipoprotein and recent observational, biological and clinical evidence strongly suggests that HDL-C is a promising target of therapeutic intervention [12,13].

Material and Methods

From June 2011 to January 2013, a total of 200 patients (100 males & 100 females) were studied. Those patients were seen in the department of nephrology in Al-Kindy Teaching Hospital, Baghdad / Iraq. The age

ranged from 45-75 years, all patients were diagnosed as having renal anemia from history, clinical examination and laboratory investigations including lipid profile TC, TG and HDL-C. Patients were given epoetin alfa (4000 IU), subcutaneously (SC) once, twice or three times a week, depending on the degree of anemia. All patients received atorvastatin 10 mg once daily along with restricted protein diet. All patients were not on dialysis.

Statistical Analysis

The Statistical Analysis System-SAS was used to detect the difference factors in study parameters (applied of completely randomized design-CRD). Duncan's test was used to find the difference factors in study parameters.*: Significant at level $P < 0.05$ / **: Highly Significant at level $P < 0.01$

A: Significant mild group with other groups at level $P < 0.05$ /

B: Significant moderate group with other groups at level $P < 0.05$ /

C: Significant severe group with other groups at level $P < 0.05$.

Results

In this study 200 CKD patients with renal anemia were given EPO treatment (4000 IU) SC. Patients depending on the response to EPO therapy were classified into two groups, rhEPO responders 160 patients (80%) and rhEPO non-responders 40 patients (20%), the two groups were divided into three sub-groups depending on degree of anemia according to the value of hemoglobin (Hb), was as follow: rhEPO responders mild anemia ($Hb \geq 10$ g/dl): four times (Month (M)1-M5) (Table 1 and 2) and two times (M6-M7) per month, moderate anemia ($8 \text{ g/dL} \leq Hb < 10 \text{ g/dL}$): four times (M1-M2), eight times (M3-M6) and four times (M7) per month and for those with severe anemia ($Hb < 8 \text{ g/dL}$): eight times (M2-M6) and four times (M7) per month. For those

Groups Months	Mild (NO:36) Mean \pm S.D. BC	Moderate (NO:62) Mean \pm S.D. AC	Severe (NO:42) Mean \pm S.D. AB
M1	10.18 \pm 0.26 BC	8.59 \pm 0.45 AC	6.54 \pm 0.39 AB
M2	10.57 \pm 0.59 ** BC	9.35 \pm 0.44 ** AC	8.14 \pm 0.91 ** AB
M3	10.91 \pm 0.48 ** BC	9.91 \pm 0.57 ** AC	8.84 \pm 1.03 ** AB
M4	11.45 \pm 0.53 ** BC	10.56 \pm 0.63 ** AC	9.48 \pm 0.98 ** AB
M5	12.00 \pm 0.53 ** BC	11.09 \pm 0.74 ** AC	10.19 \pm 0.88 ** AB
M6	12.56 \pm 0.48 ** BC	11.67 \pm 0.78 ** AC	10.89 \pm 0.88 ** AB
M7	13.29 \pm 0.65 ** BC	12.23 \pm 0.77 ** AC	11.58 \pm 0.93 ** AB

Table 1: Comparison of Hb between rhEPO responders patients.

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Received August 16, 2013; Accepted September 17, 2013; Published September 21, 2013

Citation: Al-Saedi AJH, Alwachi SN, Karim AHA(2013) Effect of Erythropoietin Therapy on the Lipid Profile in Patients with Chronic Kidney Disease – A Single Center Study. J Nephrol Ther 3: 140. doi:10.4172/2161-0959.1000140

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Groups Months	Mild (NO:36) Mean ± S.D. BC	Moderate (NO:62) Mean ± S.D. BC	Severe (NO:42) Mean ± S.D. AB
M1	32.56 ± 0.84 BC	27.84 ± 1.36 BC	21.57 ± 1.23 AB
M2	33.78 ± 1.89 ** BC	30.11 ± 1.34 ** BC	26.47 ± 2.69 ** AB
M3	34.78 ± 1.42 ** BC	31.81 ± 1.74 ** BC	28.62 ± 3.09 ** AB
M4	36.44 ± 1.59 ** BC	33.74 ± 1.90 ** BC	30.48 ± 2.91 ** AB
M5	38.00 ± 1.51 ** BC	35.32 ± 2.23 ** BC	32.67 ± 2.66 ** AB
M6	39.78 ± 1.46 ** BC	37.09 ± 2.32 ** BC	34.71 ± 2.69 ** AB
M7	41.83 ± 1.92 ** BC	38.74 ± 2.35 ** BC	36.76 ± 2.88 ** AB

Table 2: Comparison of Hct between rhEPO responder patients.

Groups Months	Mild (NO:36) Mean ± S.D. BC	Moderate (NO:62) Mean ± S.D. AC	Severe (NO:42) Mean ± S.D. AB
M1	240.53 ± 18.39 BC	225.32 ± 20.54 AC	168.10 ± 14.24 AB
M2	221.67 ± 20.94 ** C	213.52 ± 24.04 ** C	162.26 ± 14.24 AB
M3	209.83 ± 25.23 ** C	209.05 ± 23.46 ** C	159.81 ± 13.71 ** AB
M4	199.56 ± 27.07 ** C	205.29 ± 23.22 ** C	158.67 ± 12.85 ** AB
M5	194.78 ± 26.91 ** C	199.23 ± 21.55 ** C	157.02 ± 11.77 ** AB
M6	186.39 ± 24.43 ** C	194.56 ± 21.26 ** C	154.93 ± 11.90 ** AB
M7	180.17 ± 20.80 ** BC	190.18 ± 21.77 ** AC	154.12 ± 10.83 ** AB

Table 3: Comparison of cholesterol between rhEPO responders patients.

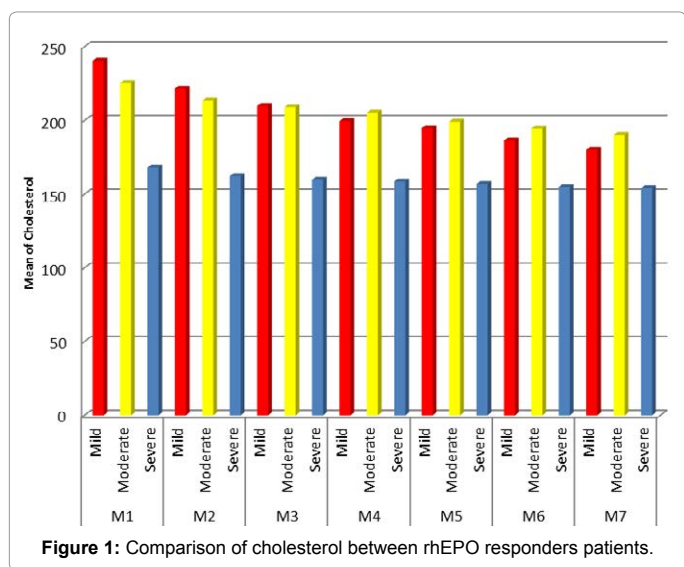


Figure 1: Comparison of cholesterol between rhEPO responders patients.

who were rhEPO non- responders mild anemia: four times (M1-M4), eight times (M5-M6) and twelve times (M7) per month, moderate anemia: four times (M1-M2), eight times (M3-M5) and twelve times (M6-M7) per month and those with severe anemia: eight times (M1-M4) and twelve times (M5-M7) per month. EPO dose (4000 IU syringe

SC). In the rhEPO responders results showed increase in Hb (g/dl), haematocrit (Hct) (%) and HDL-C (mg/dl) with decrease in TC (mg/dl), TG (mg/dl) levels during the period of EPO therapy (Table 3 and Figure 1) showed significant difference (P<0.05) in the mean TC (mg/dl) of mild (M1& M7), moderate (M1&M7) and severe (M1&M7) anaemia groups were (240.53 ± 18.39 & 180.17 ± 20.80), (225.32 ± 20.54 & 190.18 ± 21.77) and (168.10 ± 14.24 & 154.12 ± 10.83) respectively. While contrast significant differences were observed for the other month among all anaemia groups. The levels of TC (mg/dl) before therapy (M1) and after therapy (M2-M7) showed significant difference (P<0.01) in mild anaemia (240.53 ± 18.39) and (221.67 ± 20.94M2-180.17 ± 20.80M7), moderate anaemia (225.32 ± 20.54) and (213.52 ± 24.04M2-190.18 ± 21.77M7) and severe anaemia groups (168.10 ± 14.24) and (162.26 ± 14.24M2- 154.12 ± 10.38M7) respectively.

(Table 4 and Figure 2) showed significant difference (P<0.05) in the mean TG (mg/dl) of mild (M1- M2), moderate (M1-M2) and severe (M1- M2) anaemia groups were (173.28 ± 6.17-169.42 ± 7.18), (167.02 ± 14.82 ± 14.82-163.95 ± 14.06) and (158.55 ± 5.39-156.50 ± 5.64) respectively. While contrast significant differences were observed for the other month among all anaemia groups. The levels of TG (mg/dl) before therapy (M1) and after therapy (M2-M7) showed significant difference (P<0.01) in mild anaemia (173.28 ± 6.17) and (166.14 ± 7.83M3 -

Groups Months	Mild (NO:36) Mean ± S.D. BC	Moderate (NO:62) Mean ± S.D. AC	Severe (NO:42) Mean ± S.D. AB
M1	173.28 ± 6.17 BC	167.02 ± 14.82 AC	158.55 ± 5.39 AB
M2	169.42 ± 7.18 * BC	163.95 ± 14.06 AC	156.50 ± 5.64 AB
M3	166.14 ± 7.83 ** C	162.81 ± 13.42 C	155.00 ± 6.19 ** AB
M4	162.94 ± 7.51 ** C	161.61 ± 13.26 * C	152.07 ± 6.08 ** AB
M5	159.64 ± 7.61 ** C	159.60 ± 13.58 ** C	149.55 ± 6.48 ** AB
M6	156.03 ± 8.38 ** C	157.40 ± 13.42 ** C	146.79 ± 6.00 ** AB
M7	152.64 ± 8.57 ** C	154.03 ± 13.31 ** C	143.81 ± 6.15 ** AB

Table 4: Comparison of triglyceride between rhEPO responders patients.

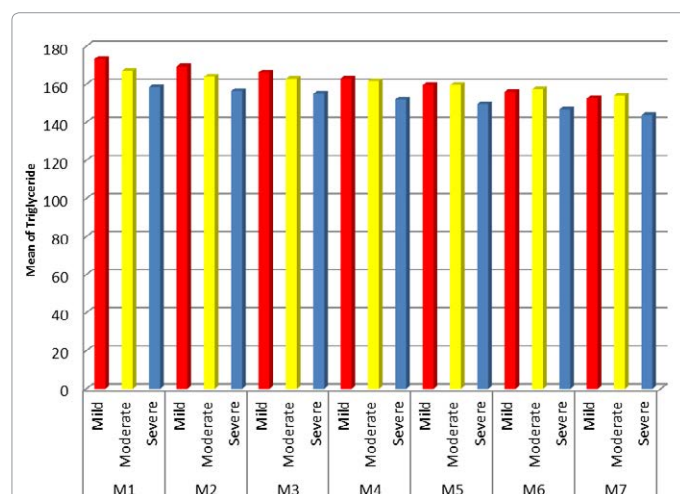
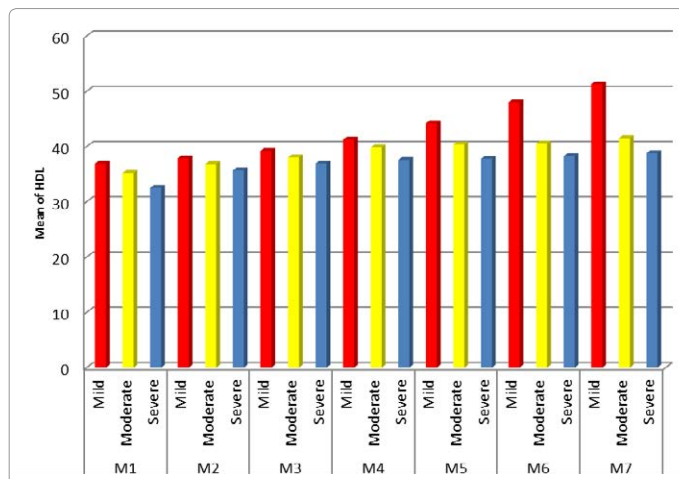


Figure 2: Comparison of triglyceride between rhEPO responders patients.

Groups Months	Mild (NO:36) Mean ± S.D.	Moderate (NO:62) Mean ± S.D.	Severe (NO:42) Mean ± S.D.
M1	36.89 ± 1.91 C	35.21 ± 2.24 C	32.50 ± 8.57 AB
M2	37.86 ± 2.55 C	36.82 ± 2.41 ** C	35.67 ± 2.68 * AB
M3	39.19 ± 3.18 ** C	38.03 ± 2.56 ** C	36.90 ± 3.18 ** A
M4	41.25 ± 3.40 ** BC	39.85 ± 2.96 ** AC	37.57 ± 2.89 ** AB
M5	44.22 ± 4.22 ** BC	40.37 ± 3.17 ** AC	37.76 ± 3.27 ** AB
M6	48.00 ± 4.96 ** BC	40.55 ± 3.36 ** AC	38.24 ± 3.26 ** AB
M7	51.28 ± 5.17 ** BC	41.50 ± 3.28 ** AC	38.79 ± 2.95 ** AB

Table 5: Comparison of HDL between rhEPO responders patients.



In the rhEPO non-responders results showed decrease in Hb (g/dl) and Hct(%)levels .There was no change in TC (mg/dl), TG (mg/dl) and HDL-C (mg/dl) levels during the period of EPO therapy.

Figure 3: Comparison of HDL between rhEPO responders patients.

Groups Months	Mild (NO:8) Mean ± S.D.	Moderate (NO:26) Mean ± S.D.	Severe (NO:26) Mean ± S.D.
M1	10.89 ± 0.87 BC	8.86 ± 0.51 AC	6.46 ± 0.56 AB
M2	11.41 ± 1.16 BC	9.39 ± 0.66 ** AC	7.96 ± 0.62 ** AB
M3	9.90 ± 1.07 C	9.47 ± 1.07 * C	8.36 ± 1.41 ** AB
M4	10.45 ± 1.48 C	9.66 ± 1.43 * C	8.89 ± 1.80 ** A
M5	9.95 ± 1.17 BC	8.64 ± 1.48 A	8.21 ± 1.76 ** A
M6	9.08 ± 1.36 ** C	8.05 ± 1.10 ** C	7.36 ± 1.53 ** A
M7	8.01 ± 0.95 ** C	6.61 ± 1.42 ** C	5.67 ± 1.27** AB

Table 6: Comparison of Hb between rhEPO non-responder patients.

152.64 ± 8.57 M7), moderate anaemia (167.02 ± 14.82) and (159.60 ± 13.58M5–154.03 ± 13.31M7) and severe anaemia groups (158.55 ± 5.39) and (155.00 ± 6.19M3 – 143.81 ± 6.15M7) respectively.

Table 5 and Figure 3 showed significant difference (P<0.05) in the mean HDL (mg/dl) of mild (M4- M7), moderate (M4-M7) and severe

(M4- M7) anaemia groups were (41.25 ± 3.40–51.28 ± 5.17), (39.85 ± 2.96–41.50 ± 3.28) and (37.57 ± 2.89–38.79 ± 2.95) respectively. While significant differences were observed for the other months among all anaemia groups. The levels of HDL (mg/dl) before therapy (M1) and after therapy (M2-M7) showed significant difference (P<0.01) in patients with mild anaemia (36.89 ± 1.91) and (39.19 ± 3.18 M3–51.28 ± 5.17 M7), moderate anaemia (35.21 ± 2.24) and (36.82 ± 2.41 M2–41.50 ± 3.28 M7) and severe anaemia groups (32.50 ± 8.57) and (36.90 ± 3.18 M3 - 38.79 ± 2.95) M7 respectively (Tables 6-10).

Groups Months	Mild (NO:8) Mean ± S.D.	Moderate (NO:26) Mean ± S.D.	Severe (NO:26) Mean ± S.D.
M1	32.13 ± 5.19 BC	28.31 ± 1.38 AC	21.96 ± 0.99 AB
M2	34.75 ± 3.41 BC	30.04 ± 2.03 ** AC	25.46 ± 2.04 ** AB
M3	31.75 ± 3.88 C	30.31 ± 2.98 ** C	29.25 ± 3.86 ** AB
M4	33.00 ± 4.44 C	30.92 ± 4.39 ** C	29.04 ± 4.94 ** A
M5	31.50 ± 4.04 C	28.00 ± 4.55 C	26.81 ± 5.28 ** A
M6	28.63 ± 3.70 C	25.96 ± 3.12 * C	24.12 ± 4.60 * A
M7	25.38 ± 2.62 ** C	23.46 ± 2.76 ** C	19.00 ± 4.55** AB

Table 7: Comparison of Hct between rhEPO non-responder patients.

Groups Months	Mild (NO:8) Mean ± S.D.	Moderate (NO:26) Mean ± S.D.	Severe (NO:26) Mean ± S.D.
M1	252.13 ± 22.34 BC	231.65 ± 10.27 AC	173.77 ± 26.88 AB
M2	249.00 ± 20.06 C	231.04 ± 9.67 C	174.42 ± 28.56 AB
M3	251.38 ± 19.72 BC	230.46 ± 11.69 AC	174.50 ± 28.81 AB
M4	249.51 ± 18.44 BC	230.46 ± 12.43 AC	172.58 ± 30.17 AB
M5	248.38 ± 20.43 BC	229.96 ± 13.83 AC	170.81 ± 31.99 AB
M6	245.91 ± 26.89 BC	227.01 ± 13.74 AC	168.04 ± 34.51 AB
M7	243.1 ± 31.21 BC	223.34 ± 12.76 AC	165.08 ± 37.56 AB

Table 8: Comparison of cholesterol between rhEPO non-responder patients.

Groups Months	Mild (NO:8) Mean ± S.D.	Moderate (NO:26) Mean ± S.D.	Severe (NO:26) Mean ± S.D.
M1	167.50 ± 6.82 C	165.92 ± 7.59 C	145.73 ± 7.88 AB
M2	167.58 ± 5.63 C	165.54 ± 8.06 C	144.00 ± 7.40 AB
M3	167 ± 4.58 C	165.73 ± 7.34 C	144.38 ± 7.83 AB
M4	167 ± 10.03 C	165.88 ± 8.94 C	143.54 ± 8.44 AB
M5	166.88 ± 10.83 BC	164.00 ± 9.35 AC	143.34 ± 8.63 AB
M6	166.53 ± 12.46 BC	164.58 ± 9.67 AC	143.38 ± 7.82 AB
M7	166 ± 14.99 BC	163.42 ± 9.74 AC	142.52 ± 8.15 AB

Table 9: Comparison of triglyceride between rhEPO non-responder patients.

Groups Months	Mild (NO:8) Mean ± S.D.	Moderate (NO:26) Mean ± S.D.	Severe (NO:26) Mean ± S.D.
M1	36.75 ± 1.04 C	36.00 ± 0.94 C	35.12 ± 0.99 AB
M2	36.88 ± 0.83 C	36.01 ± 1.13 C	35.15 ± 0.78 AB
M3	37.00 ± 1.85 C	36.25 ± 1.17 C	35.21 ± 1.34 AB
M4	37.21 ± 3.49 C	36.41 ± 1.59 C	35.34 ± 1.80 AB
M5	37.35 ± 2.71 BC	36.63 ± 1.81 AC	35.5 ± 1.68 AB
M6	37.35 ± 1.31 BC	36.30 ± 1.79 AC	34.95 ± 1.99 AB
M7	37.10 ± 1.41 BC	35.69 ± 2.04 AC	34.65 ± 3.54 AB

Table 10: Comparison of HDL between rhEPO non-responders patients.

Discussion

In our study, cholesterol was lower in rhEPO responders than rhEPO non – responders patients, also cholesterol level is positively associated with improvement of anemia in CKD patients. This is similar with Tanaka et al., Manitius et al., Mak et al. and Ponnudhali and Nagarajan [14-18] showed that EPO therapy is associated with an improvement in the blood lipid profile especially cholesterol and LDL – C in CKD patients and in complement with Allegra et al. and Nissenson and Fine [19,20] suggested that long – term treatment with EPO altered total serum cholesterol and LDL – C in patients. However, this effect is influenced significantly by food intake.

Triglyceride was lower in rhEPO responders than rhEPO non – responders patients, also TG level is positively associated with EPO therapy in CKD patients. This is similar with Pollock et al., Jamil and Naqvi, Bugeja and Chan and Naini et al. [21-24] showed that long – term rhEPO treatment is associated with an improvement in the TG levels.

High density lipoprotein was higher in rhEPO responders than rhEPO non – responders patients, also HDL level is positively associated with EPO therapy in CKD. This is compatible with other studies Papavasiliou et al, Siamopoulos et al. and Tselepis and Siamopoulos [25-27] suggested that, EPO treatment of predialysis patients with CKD significantly increases serum HDL – C levels and HDL – C / LDL – C, which may represent an important anti atherogenic effect of this hormone. In CKD, epoetin alfa improves quality of life, physical activity and increased tissue oxygenation that lead to an increase in activity of several enzymes and transferring proteins involved in HDL-C biogenesis as well as in HDL maturation and lead to the increase in HDL-C levels [27,28].

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