Original Article

Gender Differences in Dose of Erythropoietin to Maintain Hemoglobin Target in Hemodialysis Patients

Abstract

Dialysis patients receiving erythropoietin (EPO) for anemia management are a challenge due to the significant interindividual variability in erythropoietic response. Our objective was to determine if there is a gender-dependent difference in the EPO doses required to maintain the hemoglobin (Hb) targets in adult patients undergoing hemodialysis. We conducted a historic cohort study with a 12-month follow-up. We include patients with the Hb target, normal serum albumin, and normal transferrin saturation index. Monthly data were gathered for the following: Hb level, EPO doses, and intravenous iron doses. In the 11 hemodialysis facilities included, 1844 patients were on hemodialysis. We considered 389 patients for follow-up, 190 of which were excluded mainly for failing to keep the Hb level in the established range. The final cohort for analysis included 141 men (70.9%) and 58 women (29.1%). At baseline, men weighed more than women ($P < 0.001$). At the end of the follow-up period, the EPO required to maintain Hb level between 10 and 13 g/dl was significantly higher in women in the monthly dose, weekly dose, and weekly EPO dose/patient weight, with no difference in the monthly iron dose. There was a significant association between female gender and the use of high EPO doses (odds ratio, 4.1; 95% confidence interval, 1.4–12.2; $P = 0.01$). Our study demonstrates that women require higher doses of EPO to achieve Hb targets.

Keywords: *Erythropoietin, gender, hemodialysis, hemoglobin target*

J. A. Coronado Daza, G. Urrútia Cuchi[1]

Faculty of Medicine, Medical Department, University of Cartagena, Cartagena, Colombia, [1]Sant Pau Biomedical Research Institute, Barcelona, Spain

Introduction

Anemia is a frequent complication of the chronic kidney disease (CKD). The origin of anemia is multifactorial but is mainly due to a deficient erythropoietin (EPO) production at a renal level. Anemia is associated with increased cardiovascular morbidity and mortality, kidney disease progression, and less quality of life.[1-3] Since 1989, recombinant human EPO has transformed the treatment of renal anemia, aimed at reducing transfusions and enhancing quality of life and survival.[4-6] Currently, anemia guidelines on hemoglobin (Hb) targets have recommended an Hb level of 11–12 g/dl in patients with CKD, 13 g/dl being the maximum level, based mainly on the TREAT study.[7-10]

The requirements of higher doses of EPO are mainly associated to iron deficiency and chronic inflammation; other causes are malnutrition, secondary hyperparathyroidism, type of vascular access, age, time in dialysis, and gender.[11,12] Most studies assessing the response to EPO and other erythropoiesis-stimulating agents (ESAs) have focused on modifiable factors such as iron deficiency and dialysis doses. Nonmodifiable factors such as gender, CKD etiology, and age have not been sufficiently studied.[13] In medical literature, several reports found that women receive higher doses of ESAs for the treatment of anemia.[14-19] Our objective was to determine if there is a gender-dependent difference in the EPO doses required to maintain Hb target in adult patients with CKD undergoing hemodialysis.

Methods

We conducted a historic cohort study in patients undergoing chronic hemodialysis treatment in Northern Colombia from March 01, 2013 to May 31, 2014. The study was approved by the Institution Research Ethics Committee, and due to the nonintrusive nature of the research, a written consent form was not required. Data were obtained from the electronic medical records, which include a complete register of demographic, clinical, and paraclinical characteristics.

How to cite this article: Coronado Daza JA, Cuchi GU. Gender differences in dose of erythropoietin to maintain hemoglobin target in hemodialysis patients. Indian J Nephrol 2019;29:160-5.

Address for correspondence:
Dr. J. A. Coronado Daza, Barrio Castillogrande Calle 6 No. 12-66, Edificio Sofia, Apartamento 502, Cartagena, Colombia. E-mail: jocodada@yahoo.es

Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_124_18

Quick Response Code:

The study was conducted in two stages: the initial stage lasted 3 months, during which information was gathered. This information included age, gender, weight, body mass index (BMI), hemodialysis vintage, number of hemodialysis sessions in a week, hemodialysis modality, type of filter, use of EPO for anemia treatment, serum albumin level, transferrin saturation index (TSI), and monthly Hb, considering the mean Hb as baseline value. Based on these data, inclusion criteria were adult patients on conventional chronic hemodialysis (≥3 months), with arteriovenous native fistulae, three sessions per week, using high-flow filters according to body surface, undergoing treatment with EPO, with baseline Hb ≥ 10 g/dl and ≤13 g/dl (Hb target), TSI ≥25%, and serum albumin ≥4 g/dl. Patients with viral hepatitis, autoimmune hepatitis, neoplasia, arteriovenous synthetic graft, and tunneled-catheter or temporary catheter as vascular access were excluded.[20] The second stage of the study lasted 12 months and was named the follow-up stage. During this stage, monthly data were gathered on the following: Hb level, EPO doses, and intravenous iron doses. In addition, data on serum albumin and TSI were gathered at the end of the follow-up. The average monthly measurements of Hb, EPO doses, and iron doses were used to determine the final Hb, monthly iron doses, monthly EPO (mEPO) doses, weekly EPO (wEPO) doses, patient's weight-adjusted wEPO, and EPO resistance index (ERI). In the follow-up, the following patients were excluded: those who required hospitalization for over 7 days for any cause, or hospitalization for up to 7 days due to melena episodes, hematemesis, or acute hemorrhagic events; patients with melena episodes, hematemesis, or acute hemorrhagic events that did not require hospitalization; patients with infectious process of ambulatory care that required an increase higher than 25% of the EPO doses; and patients that failed to maintain their Hb target for more than 2 months during follow-up.

The outcomes of interest were the wEPO dose divided by patient weight (in kg) (wEPO/kg), the mEPO dose, the wEPO dose, the use of wEPO/kg dose ≥120 IU/kg – considered as a high EPO (hEPO) dose, and the ERI (wEPO/kg divided by patient mean Hb level). Blood samples were collected before the beginning of hemodialysis. Hb level was measured monthly; TSI and serum albumin were determined at baseline and at the end of follow-up. The lab tests were completed by external providers using standardized techniques for sample extraction and transportation. Samples were processed using automatic and standardized methods.

Statistical analysis

We applied descriptive statistics for categorical variables, expressing them as frequency, percentage, mean, and median in accordance to each of the variables. To establish the differences in the continuous variable, we used Student's *t*-test or Mann–Whitney *U* test according to the type of data. We used the Chi-square or the Fisher test to establish hEPO dose associated according to gender. Confidence intervals were expressed at 95% and a *P* value <0.05 was considered significant.

Results

The 11 hemodialysis facilities in Northern Colombia had 1844 patients on chronic intermittent hemodialysis. After applying our inclusion and exclusion criteria, 389 of them were included for follow-up: 268 men (68.9%) and 121 women (31.1%). During 12 months of follow-up, 190 patients (48.8%) were excluded, mainly for failing to maintain the Hb target. The final cohort for analysis was of 199 patients [Figure 1].

Table 1 shows the baseline characteristics of the studied population, laboratory results at baseline and at the end of the follow-up period, the iron doses, and the EPO doses. The mean age was 55.8 years for men and 55.9 years for women ($P = 0.96$). When comparing the variables at baseline according to the patients' gender, we found that men had a significantly higher weight (68 vs. 58 kg; $P < 0.001$) and TSI (34% vs. 32%; $P = 0.02$) than women. At the end of the follow-up stage, the EPO required to maintain the Hb target was significantly higher in women than men in mEPO doses (19,168 vs. 15,667 IU, respectively; $P = 0.005$), wEPO doses (4472 vs. 3656 IU, respectively; $P = 0.02$), and wEPO/kg (74.6 vs. 55.2 IU/kg, respectively; $P < 0.001$). The ERI was significantly higher in women, and there were no differences in the monthly iron dose.

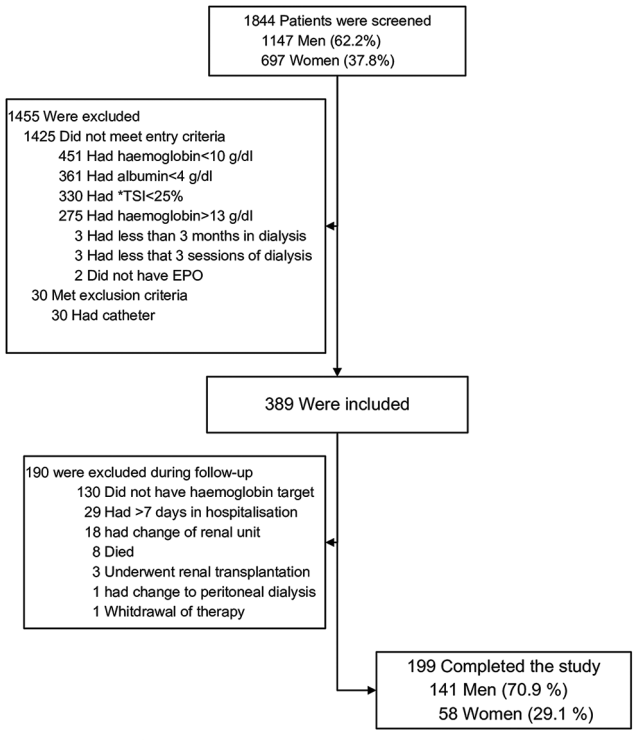

Figure 1: Screening and follow-up

Table 1: Baseline demographic, baseline laboratory data, laboratory data, and erythropoietin dose at the end of follow-up

Variables	Gender			≥120 IU/kg/week†			<120 IU/kg/week‡		
	Men	Women	*P*	Men	Women	*P*	Men	Women	*P*
Patients, *n* (%)	14 (70.9)	58 (29.1)	<0.001	6 (4.3)	9 (15.5)	0.02	13 (95.7)	49 (84.5)	0.02
Age (years)	55.8±14.6	55.9±14.1	0.96	63.3±13.4	51.7±15.2	0.14	55.5±14.6	56.7±13.9	0.60
Weight (IQR) (kg)	68 (61-75)	58 (50-68)	<0.001	62.5±8.6*	50.8±9.3*	0.02	68 (61-76)	62 (50-69)	<0.001
Body mass index (IQR) (kg/m^2)	25.5 (21.5-26.5)	23.7 (20.7-26.6)	0.22	23.5±4.2*	20.7±3.9*	0.20	24.4 (21.7-26.7)	23.7 (20.7-26.6)	0.88
Hemodialysis vintage (IQR) (years)	3.3 (2.0-6.4)	5.4 (3.5-7.9)	0.06	4.0±2.9*	6.4±3.4*	0.18	3.3 (2.0-6.4)	5.4 (3.5-7.9)	0.004
Baseline Hb (g/dl)	11.7±0.6	11.7±0.8	0.82	11.2±0.9	11.4±0.9	0.66	11.7±0.6	11.7±0.8	0.98
Baseline TSI (IQR) (%)	34 (30-43)	32 (25-41)	0.02	30.0±3.4*	32.6±8.1*	0.48	34 (30-45)	32 (29-36)	0.03
Baseline albumin (IQR) (g/dl)	4.4 (4.2-4.6)	4.3 (4.2-4.5)	0.56	4.7±0.2*	4.3±0.2*	0.01	4.4 (4.2-4.6)	4.3 (4.2-4.4)	0.16
Final Hb (g/dl)	11.6±0.5	11.4±0.5	0.08	11.0±0.4	11.2±0.5	0.42	11.6±0.5	11.5±0.5	0.12
Final TSI (IQR) (%)	32 (28-36)	30.5 (25-38)	0.44	27.8±7.8*	28.8±7.6*	0.82	32 (25-41)	31 (26-38)	0.58
Final albumin (g/dl)	4.3±0.3	4.2±0.3	0.26	4.2±0.4	4.2±0.2	0.72	4.3±0.3	4.2±0.3	0.42
Monthly EPO dose (IQR) (IU)	15,667 (11,000-21,500)	19,168 (12,833-25,000)	0.005	36,722±7393*	29,648±6544*	0.03	15,500 (10,833-21,167)	17,167 (11,833-23,167)	0.12
Weekly EPO dose (IQR) (IU)	3656 (2567-5017)	4472 (2994-5833)	0.02	8569±1725*	6918±1527*	0.03	3617 (2528-4939)	4006 (2761-5406)	0.12
EPO dose week/kg (IQR) (IU/kg/week)	57.3 (36.5-77.8)	74.6 (48.5-105.4)	<0.001	137.3±19.9*	136.4±17.4*	0.46	54.9 (36.3-73.2)	68.7 (45.8-91.1)	0.01
Monthly iron dose (IQR) (mg)	75 (33-117)	75 (17-117)	0.78	80.6±53.1*	58.3±53.9*	0.44	75 (33-113)	75 (25-117)	0.92
ERI (IQR) (week/kg/g per 100 ml Hb) (IU)	5 (3.3-6.9)	6.7 (4.1-9.2)	0.004	12.5±2.0*	12.1±1.7*	0.36	4.9 (3-6.5)	5.9 (3.9-8.4)	0.01

*Mean; †high EPO dose; ‡usual EPO dose. IQR: Interquartile range; Hb: Hemoglobin; TSI: Transferrin saturation index; EPO: Erythropoietin; ERI: Resistance to EPO index

High erythropoietin doses according to gender

Data of patients that required hEPO doses are summarized in Table 1. Those who required hEPO doses were 15.5% women and 4.3% men (P = 0.02). There was a significant association between female gender and the use of hEPO doses (odds ratio, 4.1; 95% confidence interval, 1.4–12.2; P = 0.01). When comparing the variables at baseline, the only differences that could be found in favor of men versus women were weight (62.5 vs. 50.8 kg; P = 0.02) and serum albumin (4.7 vs. 4.3 g/dl; P = 0.01). At the end of the follow-up stage, there were no differences in Hb, TSI, or serum albumin. Doses of mEPO and wEPO were significantly higher in men. There were no differences in wEPO/kg doses, monthly iron doses, or the ERI.

Usual erythropoietin doses according to gender

Data of patients that required uEPO doses (<120 IU/kg/week) are summarized in Table 1. We found that men had a significantly higher weight (68 vs. 62 kg, respectively; P < 0.001) and TSI than women at baseline (34% vs. 32%, respectively; P = 0.03). We also found that women had a significantly higher hemodialysis vintage (5.4 vs. 3.3 years, respectively; P = 0.004), wEPO/kg dose (68.7 vs. 54.9 IU/kg/week, respectively; P = 0.01), and ERI (5.9 vs. 4.9 IU week/kg/g per 100 ml Hb, respectively; P = 0.01) than men.

When comparing all patients without gender distinction that required uEPO doses versus those who required hEPO doses, we found that patients with uEPO doses had a significantly higher weight (66 vs. 57 kg, respectively; P = 0.002), BMI (24.46 vs. 21.64 kg/m^2, respectively; P = 0.02), baseline Hb (11.73 vs. 11.34 g/dl, respectively; P = 0.03), baseline TSI (33% vs. 30%, respectively; P = 0.36), and final Hb (11.56 vs. 11.15 g/dl, respectively; P = 0.004) than those with hEPO doses. There were no differences in age, hemodialysis vintage, basal albumin, final TSI, final albumin, and iron doses.

Women receiving uEPO doses had a significantly higher weight (62 vs. 50 kg, respectively; P = 0.034) and BMI (24.62 vs. 20.69 kg/m^2, respectively; P = 0.01) than women that required hEPO doses. There were no differences in age, hemodialysis vintage, baseline, and final levels of Hb, TSI, and serum albumin. The monthly iron

dose was similar: 75 mg for women with uEPO doses and 50 mg for women with hEPO doses ($P = 0.48$).

Discussion

In this study, including 199 patients undergoing chronic hemodialysis, using EPO to maintain a range of Hb between 10 and 13 g/dl, we found that women required higher doses of mEPO, wEPO, and wEPO dose/patient weight. On the contrary, we found no differences with men in monthly iron doses. The ERI was higher in women as well. We also found a larger proportion of women requiring hEPO doses and that the risk of using hEPO doses in women was four times higher than in men.

Our findings concur with other publications observing a relation between gender and EPO requirements. A study assessing the association of anemia and survival found that the masculine gender was one of the predictors of higher levels of Hb, with an inverse relationship between Hb levels and EPO doses. Additionally, there was a direct relationship between Hb levels and levels of serum albumin, TSI, and dialysis doses.[14] Another study exploring the association between hematocrit levels and changes in the prescribed doses of EPO found that male patients achieved better hematocrit levels with smaller doses of EPO. Higher hematocrit level was also associated with longer dialysis, older age, and higher TSI.[15]

The hyporesponsiveness to EPO in some patients is a condition that has been studied. A study on low response to EPO found that women receive higher EPO doses to achieve the hematocrit target. It also found a higher proportion of women receiving hEPO doses, but no association between iron levels or high levels of parathyroid hormones and the use of hEPO doses.[16] Other publications have found that women require higher doses of EPO, or even that low response is associated with iron deficiency, poor nutritional state, high-turnover bone disease, and tunneled-catheter vascular access.[17-19] Unlike the referred studies that reported an association between gender and EPO doses but not as their main objective, our study's main objective was to determine if women required higher doses of EPO to maintain the Hb target. In order to do so, we paired women and men with the reported confounding variables such as iron deposits, nutritional state, type of vascular access, and dialysis doses.

Another factor considered in our study was the Hb variability in response to EPO. It has been reported that, in patients undergoing hemodialysis with ESAs for 12 months, only 3.8% of the patients maintained the Hb target, others presented brief fluctuations above (32.9%) or below (10.5%) the target, and the rest were considered to have unstable Hb (52.9%) for fluctuating above and below the target. Changes in EPO doses and hospital admissions were identified to be associated with Hb variation.[21] Another more recent study found similar results.[22] We reported patients followed up for 12 months, excluding during this period patients with unstable Hb, according to the exclusion criteria stated in the "Methods" section. By only selecting for the final report patients that maintained their Hb in the desired target and patients with brief fluctuations above or below the Hb target, we avoided the potential confusion due to the frequent adjustments in EPO doses, considering that our objective was to determine if women required higher doses of EPO.

Physiologically, women have lower Hb levels than men, which is attributed to the effect of androgens and estrogens on erythropoiesis. This occurs mainly because of the vasodilator effect that estrogens have on the kidney microvasculature, which causes a higher oxygen liberation per red blood cells mass unit at a juxtaglomerular apparatus level.[23] According to the World Health Organization, there are gender-associated differences in the Hb levels that are considered normal, as well as in the Hb thresholds used to define anemia, which is also applicable to patients with CKD.[9,24] Despite the differences between normal levels of Hb and the anemia cut-off, the current guidelines of anemia management in patients with CKD establish an Hb target with no gender distinction. A study conducted on a population that was not undergoing dialysis or receiving EPO reported that there is a higher absolute Hb level in men than in women in different stages of CKD. They proposed considering a relative gender-specific Hb level defined as the percentage of measured Hb value in relation to the normal Hb inferior limit for each gender and found that relative Hb is higher in women than in men. They considered that this finding was worth taking into account in future recommendations and suggested the establishment of a lower Hb target in women.[25] Our findings regarding the fact that women required higher doses of EPO to achieve the Hb target could be the result of considering women values of Hb levels as similar to men and might not indicate a difference in responsiveness to EPO.

Likewise, men's weight is physiologically 15% higher than women's, although the BMI is similar due to women's lower height.[26] When quantifying the doses of EPO based on the patient's weight, the higher wEPO/kg doses could be a mathematical phenomenon. Women in our study had a significantly lower weight in the physiological range. However, we conducted an exercise of increasing women's weight by 15% to avoid a physiological difference and found that there was still a significantly higher wEPO/kg dose administered to women than to men (64.8 [42.2–91.65] vs. 57.3 [36.5–77.8], respectively; $P = 0.04$). This result suggests that the higher wEPO/kg dose in women is related to a hyporesponsiveness to EPO and is not a mathematical artifice caused by the lower weight of women. Due to the fact mentioned above, higher doses of EPO in women can be caused by establishing the objective of reaching an Hb level similar to that of men.

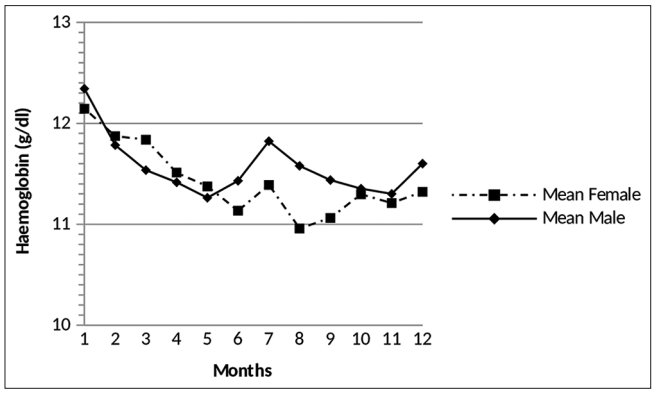

Figure 2: Hemoglobin level in the follow-up stage, according to gender

The relevance of this study is to demonstrate that women require higher doses of EPO than men to achieve the Hb target recommended by the current guidelines. In incidental patients undergoing dialysis, a longer time to achieve the Hb target has been reported to be associated with a significantly higher risk of hospitalization and mortality.[27] The initial dose of recommended wEPO in incidental patients undergoing hemodialysis is from 60 to 150 IU/kg of body weight, according to baseline Hb.[9] Our study found that the EPO dose in women is 18% higher than in men; thus, not being aware of this percentage and applying with no gender distinction the same EPO doses can lead to higher rates of hospitalization and mortality among women.

Some of the strengths of our study include that our population consisted of prevalent patients in hemodialysis, with Hb levels within the targets recommended in the different management guidelines, both at baseline and during the follow-up period of 12 months [Figure 2]. In addition, we compared gender-dependent EPO requirements, but – unlike other studies – we controlled confounding variables such as iron deficiency, nutritional deficiency, dialysis doses, wide fluctuations in EPO doses, and hospitalizations. Our study also presents some limitations: it is an observational study and the sample size is small compared to other studies that have addressed this topic – yet with different objectives and with no control of confounding variables.

Conclusion

Our study demonstrates that women require higher doses of EPO to achieve the Hb target. This is a factor that must be taken into account to estimate the initial dose in the incidental population undergoing hemodialysis and consequently reducing the risk of hospitalization and death. Further studies are required to define if the Hb target in women undergoing dialysis should be lower than that in men.

Acknowledgment

We acknowledge the assistance of the Iberoamerican Cochrane Centre during the development of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, *et al.* The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501-10.
2. Rossert J, Froissart M. Role of anemia in progression of chronic kidney disease. Semin Nephrol 2006;26:283-9.
3. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: The atherosclerosis risk in communities (ARIC) study. Am Heart J 2006;151:492-500.
4. Eschbach JW. The anemia of chronic renal failure: Pathophysiology and the effects of recombinant erythropoietin. Kidney Int 1989;35:134-48.
5. Glaspy JA. Erythropoietin in cancer patients. Annu Rev Med 2009;60:181-92.
6. Foley RN, Curtis BM, Parfrey PS. Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: A randomized trial. Clin J Am Soc Nephrol 2009;4:726-33.
7. Locatelli F, Covic A, Eckardt KU, Wiecek A, Vanholder R; ERA-EDTA ERBP Advisory Board, *et al.* Anaemia management in patients with chronic kidney disease: A position statement by the anaemia working group of European renal best practice (ERBP). Nephrol Dial Transplant 2009;24:348-54.
8. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-32.
9. KDIGO Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335.
10. Locatelli F, Aljama P, Canaud B, Covic A, De Francisco A, Macdougall IC, *et al.* Target haemoglobin to aim for with erythropoiesis-stimulating agents: A position statement by ERBP following publication of the trial to reduce cardiovascular events with aranesp therapy (TREAT) study. Nephrol Dial Transplant 2010;25:2846-50.
11. Jairam A, Das R, Aggarwal PK, Kohli HS, Gupta KL, Sakhuja V, *et al.* Iron status, inflammation and hepcidin in ESRD patients: The confounding role of intravenous iron therapy. Indian J Nephrol 2010;20:125-31.
12. Gilbertson DT, Peng Y, Arneson TJ, Dunning S, Collins AJ. Comparison of methodologies to define hemodialysis patients hyporesponsive to epoetin and impact on counts and characteristics. BMC Nephrol 2013;14:44.
13. Ifudu O. Patient characteristics determining rHuEPO dose requirements. Nephrol Dial Transplant 2002;17 Suppl 5:38-41.
14. Madore F, Lowrie EG, Brugnara C, Lew NL, Lazarus JM, Bridges K, *et al.* Anemia in hemodialysis patients: Variables affecting this outcome predictor. J Am Soc Nephrol 1997;8:1921-9.
15. Coladonato JA, Frankenfield DL, Reddan DN, Klassen PS, Szczech LA, Johnson CA, *et al.* Trends in anemia management among US hemodialysis patients. J Am Soc Nephrol 2002;13:1288-95.
16. Eschbach JW, Varma A, Stivelman JC. Is it time for a paradigm

shift? Is erythropoietin deficiency still the main cause of renal anaemia? Nephrol Dial Transplant 2002;17 Suppl 5:2-7.
17. Gascón A, Virto R, Lou LM, Pernaute R, Moreno R, Pérez J, *et al.* Study of immutable variables determining rHuEPO dose requirements on hemodialysis patients. Nefrologia 2005;25:535-42.
18. López-Gómez JM, Portolés JM, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int Suppl 2008;74 Suppl 111:S75-81.
19. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, *et al.* Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. Am J Kidney Dis 2009;53:823-34.
20. Zumrutdal A, Sezgin N. The relationship between anemia, liver disease, and hepcidin levels in hemodialysis patients with hepatitis. Indian J Nephrol 2012;22:415-8.
21. Portolés JM, de Francisco AL, Górriz JL, Martínez-Castelao A, López-Gómez JM, Arias M, *et al.* Maintenance of target hemoglobin level in stable hemodialysis patients constitutes a theoretical task: A historical prospective study. Kidney Int Suppl 2008;74 Suppl 111:S82-7.
22. Gilbertson DT, Hu Y, Peng Y, Maroni BJ, Wetmore JB. Variability in hemoglobin levels in hemodialysis patients in the current era: A retrospective cohort study. Clin Nephrol 2017;88:254-65.
23. Murphy WG. The sex difference in haemoglobin levels in adults – Mechanisms, causes, and consequences. Blood Rev 2014;28:41-7.
24. Benoist B, McLean E, Egli I, Cogswell M. Worldwide Prevalence of Anaemia 1993-2005: WHO Global Database on Anaemia. Geneva: World Health Organization; 2008.
25. Duncan JA, Levin A. Sex, haemoglobin and kidney disease: New perspectives. Eur J Clin Invest 2005;35 Suppl 3:52-7.
26. Ogden CL, Fryar CD, Carroll MD, Flegal KM. Mean body weight, height, and body mass index, United States 1960-2002. Adv Data 2004;347:1-7.
27. Ishani A, Guo H, Gilbertson DT, Liu J, Dunning S, Collins AJ, *et al.* Time to target haemoglobin concentration (11 g/dl) – Risk of hospitalization and mortality among incident dialysis patients. Nephrol Dial Transplant 2007;22:2247-55.