The relationship between hemoglobin variability and oxidative stress and inflammation in CKD

Tulay Kus[1], Ozlem Tiryaki Usalan[2], Celalettin Usalan[2]
[1]Departmen of Medical Oncology, Adıyaman University, Training and Research Hospital, Adıyaman,
[2]Department of Nephrology, Gaziantep University School of Medicine, Gaziantep, Turkey

Evaluatıon of relationship between hemoglobın variability and oxidative stress and inflammation in chronic renal failure. 49th ERA-EDTA Congress. DOI: 10.3252/pso.eu.49era.2012. Paris, FRANCE.

Abstract

Aim: Hemoglobin (Hg) variability, which is frequently seen in patients with chronic kidney disease (CKD) who undergo dialysis, has been shown to be associated with increased mortality and cardiovascular disease (CVD) , but its mechanism remains unclear. Increased oxidative stress and inflammation with uremia lead to the development of anemia. In this context, we aimed to investigate the relationship between Hb variability and oxidative stress and inflammation. Material and Method: The data of 114 patients followed by dialysis service of Gaziantep University were included in this study retrospectively. Myeloperoxidase (MPO), nitrotyrosine (NTY), total antioxidant capacity (TAC), interleukin-6 (IL-6), Hs-CRP, and plasminogen activator inhibitor-1(PAI-1) levels of the patients whom we divided into 6 groups according to their Hg variability were measured. A control group (n = 30) was also formed demographically and clinically appropriate to this group. Results: The mean MPO, NTY, IL-6, Hs-CRP, and PAI-1 levels were higher in the dialysis patients than in the control group, whereas TAC levels were lower. Prooxidant, inflammation and procoagulant activity levels were lower in the Group 6 (Hg>12) and the Group 3 (stable, Hg=11-12 gr/dl) but higher in wide Hg variable group (Group 5) and Group 1 (Hg <12 gr/dl). Discussion: Oxidative stress, inflammation, and procoagulant activity, which are associated with higher CVD and mortality were found to be high in wide Hg variable and anemic groups in patients who underwent dialysis. The present study has a valuable finding in terms of elucidating the possible mechanism of increased mortality in patients with wide variable Hg course.

Keywords

Hemoglobin Variability; Cardiovascular Disease; Oxidative Stress; Inflammation; PAI-1 Activity; Chronic Kidney Disease

DOI: 10.4328/JCAM.5912 Received: 26.05.2018 Accepted: 09.06.2018 Published Online: 10.06.2018 Printed: 01.01.2019 J Clin Anal Med 2019;10(1): 20-5
Corresponding Author: Tulay Kus, Department of Medical Oncology, Adıyaman University, Training and Research Hospital, TR-02040, Adıyaman, Turkey.
T.: +90 4162161015 F.: +90 4162161014 E-Mail: drtulaykus83@hotmail.com

Introduction

Anemia, one of the most common complications of chronic kidney disease (CKD), is one of the major etiologic factors for cardiovascular disease (CVD) risk, which is the most important cause of morbidity and mortality [1]. Positive effects of correction of anemia on cardiovascular abnormalities, especially in left ventricular hypertrophy have been shown. It has been recently reported that overcorrection of anemia increases the risk of CVD [2]. In addition to adverse effects on the clinical outcome of anemia and its overcorrection, it is known that the variability of Hg in CKD, especially in dialysis patients, has a negative effect on morbidity, hospitalization, and mortality in recent years [3-5]. In dialysis patients, Hg variability was common and 6 different Hg groups were defined in various retrospective studies: Hg level continuously lower than 11 g / dl, Hg level occasionally lower than 11 g / dl and occasionally 11-12 g / dl (variable group close to lower limit), Hg level constantly 11-12 g / dl (stable) , Hg level sometimes higher than 12 g / dl and sometimes between 11 and 12 g / dl (variable group close to upper limit), Hg level sometimes lower than 11 g / dl, occasionally over 12 g / dl and occasionally between 11 and 12 g / dl (wide Hg variable group) and hg level constantly higher than 12 g / dl (normal) [6]. The highest morbidity and mortality was reported in the anemic group and in the wide Hg variable group, while the patients with stable Hg levels between 11-12 g / dl were reported to have the lowest morbidity and mortality. The reasons for the different morbidity and mortality data and the detailed mechanisms of different hemoglobin pathways are unknown. While many factors are implicated in Hg variability, increased oxidative stress and inflammation seem to play a role in uremic patients.

On the other hand, increased oxidative stress and inflammation are one of the well-defined factors that cause an increase in endothelial dysfunction and procoagulant activity, accelerating the atherosclerotic process and increasing CVD. In this context, the levels of these abnormalities can be different in groups with varied Hg courses, which are likely to be related to the different morbidity and mortality as shown in epidemiological studies. However, there is no published work in the literature regarding this subject. In our study, we assessed prooxidant (myeloperoxidase [MPO], nitrotyrosine [NTY]), antioxidant (total antioxidant capacity [TAC]) markers and inflammation (interleukin 6 [IL-6] Hs-CRP) and procoagulation (plasminogen activator inhibitor type 1 [PAI-1] activity) markers in 6 groups of dialysis patients with different HG courses and aimed to investigate their effects on Hg variability. We suggest that evaluation of these parameters associated with higher CVD in uremic patients may provide potential information in explaining the morbidity and mortality mechanism in patients with wide Hg variability and may be the basis for future prospective studies.

Material and Method

Patients

This retrospective study was conducted in single-center of our university in Turkey. The present study was approved by the Independent Ethics Committee of our university. All procedures performed in this study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments. All patients were informed about the procedures and informed consent was obtained.

Total of 114 patients (69 females, 45 males) with end-stage renal disease (ESRD) who were on hemodialysis (HD) program for 3 days a week for 4 hours at the Nephrology Department of Gaziantep University Medical Faculty Hospital are included in our study. A control group consisted of 30 healthy (18 female, 12 male) people with matching age, gender and body mass index (BMI). The mean age of the patients with ESRD was 49.69 ± 15.4 and the control group was 49.72 ± 4.15. The average duration of dialysis in HD patients was 28 months. The causes of renal failure in the HD patient group were following: chronic glomerulonephritis in 16 patients, chronic pyelonephritis in 4 patients, obstructive uropathy in 3 patients, amyloidosis in 3 patients, polycystic kidney disease in 4 patients, HT in 36 patients and DM in 48 patients. Patients with recent past infections, collagen tissue disease, vasculitis, neoplasia, drug use affecting these HD parameters, smokers, patients using vitamin E and vitamin C were excluded from the study as these factors affect the parameters evaluated in this study.

The control group had no renal insufficiency and it was noted that the controls were similar to the patient group in terms of demographic data, DM and HT, which are known to affect oxidative stress, inflammation, and PAI-1 levels. Individuals with any drug use and who had collagen tissue disease, vasculitis, recent infection, CVD were not included in the control group. The Hg values of the HD patients for the last 6 months were retrospectively recorded and based on previous studies. HD patients were divided into following 6 groups according to the Hg course [6]: Group 1 (patients with a continuous Hg level below 11 gr/dl),

Group 2 (Hg level is occasionally between 11-12 gr/dl and occasionally below 11 gr/dl (variable group close to the lower limit)), Group 3 (with Hg level between 11-12 gr/dl),

Group 4 (Hg level was occasionally between 11-12 gr/dl and occasionally higher than 12 gr/dl (variable group close to the upper limit)), Group 5 (with wide Hg variable group), Group 6: (with continuous Hg level above 12 gr/dl).

Blood samples were taken for PAI-1 assays, routine biochemistry, complete blood count, oxidative stress markers (MPO, NTY, TAK), inflammatory markers (IL-6, Hs-CRP), and post-transfusion biomarkers, results were recorded after history and physical examination of all HD patients and control group. Blood samples were taken immediately before the dialysis session.

Measurements and Methods

Blood samples (10 ml) were taken from all the involved patients and from the control group into polypropylene tubes containing 1 ml of 0.109 m trisodium citrate and centrifuged at 4000 rpm for 10 minutes, after which the supernatant was taken up to polypropylene tubes and stored at -70 ^{OC} until the study.

Serum MPO level was measured by Immunoassay (Immunoassays AG, Bensheim, Germany), enzyme immunoassay (ELISA). NTY level was similarly determined using the ELISA method with "Bioxtech, Oxisresearch, USA" device. TAC was measured by the colometric method developed by Erel and expressed in terms of mM Trolox eq / L unit. Serum IL-6 levels were studied by the "a human IL-6 ELISA kit (Ultra Sensitive ELISA; R & D systems Inc. USA). Serum hs-CRP level was measured by a nephelometric method using the Cardiophase hs-CRP kit (mg/l) in the Dade Behring Nephelometer 100 analyzer using the precise CRP method. PAI-1 activity was measured by the "Chromogenic Assay (Biopool, Sweden)" method.

Statistics

Continuous variables were expressed as mean ± S.D. Student's t-test and Mann- Whitney U test was used to compare continuous variables whereas chi-square was used to compare categorical variables. Pearson analysis was applied in the correlation analysis. P <0.05 was considered statistically significant and analyzes were done with SPSS, version 22.

Results

When demographic and clinical data were analyzed in 114 HD patients and 30 control groups studied, there were no significant differences in terms of age, sex, body mass index, the percentage of diabetic and hypertensive patients, LDL cholesterol levels and the proportion of patients receiving antihypertensive drugs (p>0.05). Table 1 summarizes the demographic and clinical data of all patient groups and the control group.

Positive correlation was found between MPO and IL-6, Hs-CRP and PAI-1 activity (r 0.283, r 0.324, r 0.434, respectively, p <0.001), and between NTY and IL-6, Hs-CRP, PAI-1 activity (r 0.212, r 0.246, r 0.312, respectively, p<0.001) of HD patients, whereas negative correlation was detected with TAC, these parameters (IL-6, Hs-CRP and PAI-1 activity) (r –0.236, r -0.186, r, -0.386, respectively, p<0.001).

The mean levels of MPO, NTY, TAC, IL-6, Hs-CRP and PAI-1 activity were compared in the patient group and the control group (Table 2).

HD patients were divided into 6 groups according to the Hg levels as a result of the retrospective screening of last 6 months. The mean levels of oxidative stress markers (MPO, NTY, and TAC), inflammation markers (IL-6, Hs-CRP) and thrombotic-fibrinolytic system determinants (PAI-1 activity) detected in these groups are shown in Table 3.

The mean MPO levels of HD patients were higher than those of the control group (p< 0.001) In HD patient groups MPO level was the highest in Group 1 while the lowest in Group 6 (p = 0.042). The closest MPO level to group 1 was found in Group 5, which was a wide variable group (p = 0.31). The mean MPO level in Group 3 (hb: 11-12 stable) was lower than in Groups 1, 2, 4 and 5 (Figure. 1).

The mean levels of NTY were higher than the control group (p <0.001), similar to MPO. The closest value to the control group was found in Group 6 and Group 3. There was no significant difference between Group 1 and 5 NTY levels (p = 0.56) and it was significantly higher than all other groups. There was no statistically significant difference between Group 3 and 6 NTY levels (p = 0.43) but it was lower than other groups (Figure 1).

The level of TAC was significantly lower in the patient group than in the control group (p<0.001). The lowest value was detected in Group 1 while the highest value was found in Group 6 (p = 0.047). There was no significant difference between TAC levels between Group 1 and Group 5 (p = 0.46). Group 5 had TAC levels lower than Group 3, 6 and control groups. TAK levels were higher in Group 3 than Group 1, and 5 (Figure 2).

HD patient groups were higher than the control group (p <0.001). The highest value for IL-6 was found in Group 1 while the lowest value was found in Group 6 (p = 0.065). In Group 3, the IL-6 level was lower than Group 1 (p = 0.02) but higher than Group 6 (p = 0.03), however, there was no statistically difference with other groups (all parameters p> 0.05) (Figure 3).

The Hs-CRP levels of the patient groups were higher than the control group (p<0.001). The highest value among the groups was in Group 1 and the lowest value was in Group 6 (p = 0.64). Group 1 Hs-CRP levels were also significantly higher than the other groups (all p values were p <0.05), but there was no statistically significant difference in Hs-CRP levels between groups 2,3,4,5 and 6 (all p values were p> 0.05) (Figure 3).

PAI-1 activity levels in hemodialysis patients were higher than the control group (p <0.001). PAI-1 activity level was highest in group 1, while group 6 was the lowest (p = 0.032). The closest group to group 1 was group 5 while the closest group to group 6 was group 3 (p = 0.54 and p = 0.78, respectively) (Figure 2).

Table 1. Demographic and clinical data of all patient groups and the control group.

Variables	Group 1 (n=10)	Group 2 (n=32)	Group 3 (n=19)	Group 4 (n=15)	Group 5 (n=26)	Group 6 (n=12)	Control (n=30)
Age (Year)	47.33±16.62	44.66±18.42	46.53±16.45	53.40±18.5	55.23±22.5	51.00±9.16	49.72±4.15
Gender (Female/male)	8/2	23/9	15/4	6/9	12/14	5/7	18/12
BMI (kg/m^2)	28.4±2.9	27.66±3.36	28.74±4.26	27.67±2.58	27.65±3.77	27.67±2.51	26.97±3.95
Dialysis time (ay)	24±4	32±8	26±3	28±6	25±6	34±11	-
Kt/V	1.63±0.21	1.64±0.34	1.66±0.31	1.52±0.18	1.56±0.28	1.53±0.03	-
Smoke (N)	2	6	4	3	5	3	6
Diabetes mellitus (N)	5	12	9	8	10	4	10
Hypertension (N)	1	3	2	2	3	1	4
LDL (mg/dl)	108.8±42	112.6±36	106.7±24	102.6±18	105.4±32	110.3±48	108.5±72
Albumin (gr/dl)	3.72±0.8	3.78±0.6	3.84±0.4	3.82±0.7	3.92±0.8	4.01±0.6	4.02±0.8

BMI: Body mass index, Kt/V: Dialysis efficiency value, N: number

Table 2. The mean levels of oxidative stress markers, inflammation markers, and thrombotic-fibrinolytic system determinants in the patient group and the control group

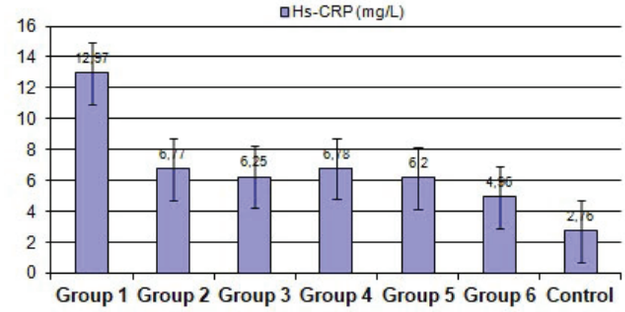
Variables	Hemodialysis patients (n=114)	Control group (n=30)	P value
Oxidative stres indicators			
MPO (ng/ml)	498.83±48.32	376.86±30.50	<0.001
NTY (nM)	16.28±2.28	10.33±0.60	<0.001
TAC (mmol Teq/L)	1.24±0.12	1.75±0.05	<0.001
Inflammation indicators			
IL-6 (pg/ml)	15.32±8.26	3.6±1.8	<0.001
Hs-CRP (mg/L)	7.32±3.48	2.76±2,45	<0.001
PAI-1 activity (IU/ml)	17.52±5.92	8.28±1.81	<0.001

MPO: myeloperoxidase, NTY: nitrotyrosine, TAC: total antioxidant capacity, IL-6: interleukin-6, Hs-CRP, PAI-1: plasminogen activator inhibitor-1

Table 3. The mean levels of oxidative stress markers, inflammation markers and thrombotic-fibrinolytic system determinants

Variables	Group 1 (n=10)	Group 2 (n=32)	Group 3 (n=19)	Group 4 (n=15)	Group 5 (n=26)	Group 6 (n=12)	Control (n=30)
Oxidative stres indicators							
MPO (ng/ml)	548.32±36.46	508.48±72.64	473.80±30.50	512.44±32.64	524.56±24.72	428.64±28.56	376.86±30.50
NTY (nM)	20.48±2.04	15.92±3.08	14.08±1.66	16.02±3.08	18.94±2.06	12.22±0.32	10.33±0.60
TAC (mmol Teq/L)	1.02±0.02	1.22±0.03	1.36±0.06	1.24±0.04	1.12±0.04	1.52±0.04	1.75±0.05
Inflammation indicators							
IL-6 (pg/ml)	24.48±1,3	15.46±8,33	14.64±7,55	14.99±2,95	16.22±4,6	6.08±1.09	3.6±1.8
Hs-CRP (mg/L)	12.97±5,25	6.77±4,26	6.25±4,25	6.78±3,18	6.2±4,0	4.96±1,89	2.76±2,45
PAI-1 activity (IU/ml)	24.36±6.22	16.62±7.76	13.76±4.48	15.98±6.56	19.96±8.31	12.54±3.72	8.28±1.81

MPO: myeloperoxidase, NTY: nitrotyrosine, TAC: total antioxidant capacity, IL-6: interleukin-6, Hs-CRP, PAI-1: plasminogen acivator inhibitor-1



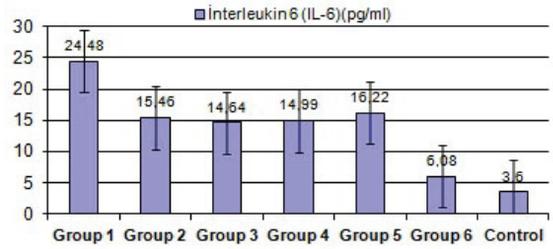
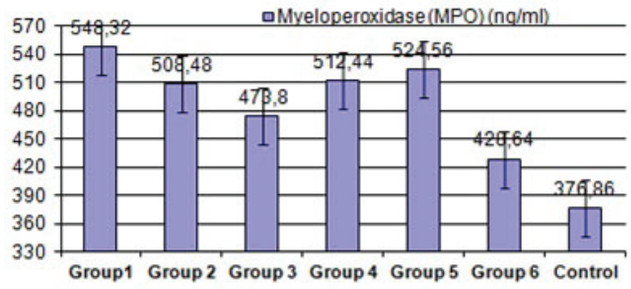


Figure 1. The graphics of mean myeloperoxidase and nitrotyrosine levels,



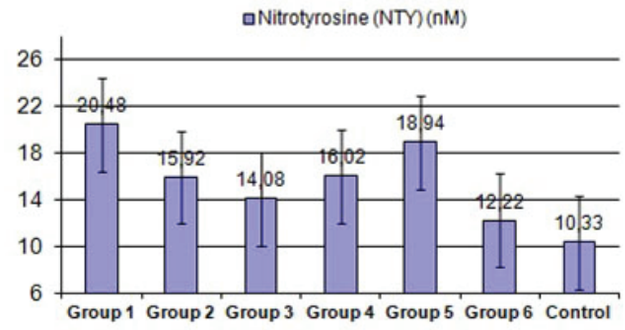
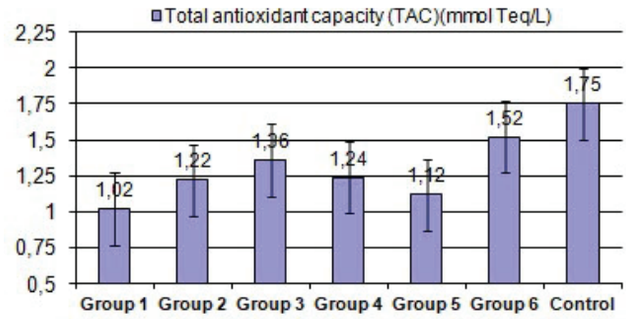


Figure 2. The graphics of mean total antioxidant capacity and plasminogen acivator inhibitor-1 levels

Discussion

It is known that uremic patients under hemodialysis treatment with anemia and Hg variability were shown to have increased hospital admission, CVD event, morbidity and mortality rates [7-10]. The relationship between oxidative stress, inflammation and increased procoagulant activity and cardiovascular disease has been described in uremic patients. Oxidative stress and inflammation determinants have not been studied in patients with different Hg variability up to now, although it is known that oxidative stress and inflammation may play a role in the development of Hg variability [11]. In this study, we examined the Hg courses in 6 groups as defined in previous studies and assessed the levels of prooxidant (MPO, NTY), antioxidant (TAC), inflammation (IL-6, Hs-CRP), procoagulation (PAI-1 activity) markers. We showed that the anemic groups and wide Hg variable group had the greatest prooxidant, inflammatory, and procoagulant markers, while the groups with stable Hg course and high Hg course had the lowest levels.



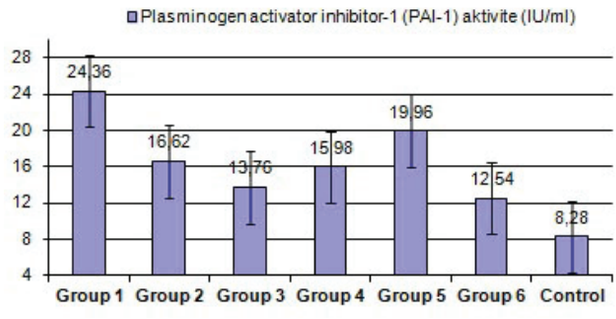


Figure 3. The graphics of mean interleukin-6, and Hs-CRP leves

It was shown that morbidity and mortality are the lowest in uremic patients with stable Hg levels between 11-12 g / dl [7]. However, there are difficulties in keeping the above-mentioned narrow ranges of Hg level in conditions with complicated pathogenesis like CKD and accompanied by many comorbid conditions. There are two major difficulties in the treatment of anemia in CKD. One of them is difficult to reach the target value, and the other is the difficulty of staying on the target. In a study conducted by Ebben et al. it was found that only 6.5% of the dialysis patients had stable Hg values during 6-month follow-up [12]. It was emphasized that many factors affecting Hg variability were identified and the most effective factors were infection, inflammation, oxidative stress, comorbid conditions and EPO and iron use habits [8].

It is well known that in chronic renal disease, the level of oxidative stress resulting from the reduction of glomerular filtration rate and the proxidan-antioxidant balance in favor of prooxidant is increased. These anomalies become more evident in patients undergoing dialysis. Patients in the HD program are at higher risk of oxidative stress increase than patients who undergo peritoneal dialysis. The extracorporeal characteristics of dialysis in patients with HD program and the uremic abnormalities as well as common risk factors such as DM, HT, and dyslipidemia associated with renal failure appear to be the most important cause of this frequency. In addition, it is known that oxidative stress levels in dialysis patients are closely related to inflammation, endothelial dysfunction, and thrombotic vascular complications [13-17]. Similar to previous studies, our study showed that prooxidant activity, which is defined by MPO and NTY levels in HD patients, is higher than the control group and that antioxidant level defined by TAC is lower than the control group in HD patients. In our study, it was also found that PAI-1 activity levels which are important determinants of thrombosis and endothelial dysfunction, and IL-6 and Hs-CRP, inflammation markers, were higher in HD patients than in the control group.

In our study, the parameters which showed oxidative stress, inflammation and thrombosis tendency of dialysis patients with stabilized Hg levels (11-12 gr/dl) defined as Group 3 were found to be closest to Group 6 (Hg> 12) and control group. The MPO, NTY, PAI-1 activity levels of this group were found to be lower than the Group 1 (anemic) and Group 5 (wide Hg variable group), whereas the TAC level was higher. Levels of IL-6 and Hs-CRP were found to be lower than Group 1 in particular. When these data are evaluated together, it is seen that stable Hg levels have more positive effects on oxidative stress, inflammation, and endothelial-thrombotic determinants compared to low and variable Hg levels. This may contribute to elucidate the unexplained mechanism of the lowest mortality level in Hg-stabilized patients, as reported in the literature in recent years. It may be assumed that this positive effect we have found in our study is due to the fact that it is not exposed to increased and decreased repetitive tissue perfusion with fixed Hg levels and that the assumed tissue may be protected from perfusion stress and impairment. Since it is considered that tissue hypoxia, oxidative stress, inflammation, endothelial dysfunction, thrombosis, fibrosis, and CVD-mortality cycle are positively affected in this group, it is essential that the markers of oxidative stress, inflammation and thrombosis are lower and the antioxidant capacity is higher. When these data are evaluated together with the fact that the mortality rate of the patient increases in dialysis patients, oxidative stress, inflammation, and PAI-1 elevation are related to mortality and antioxidant treatment decreases mortality, it is clear that it will provide important contributions to explain the cause of low mortality seen at stable Hg levels.

In our study, 22.8% of the patients showed broad fluctuations of Hg level. There are many reasons for this. In our study, the levels of MPO, NTY, IL-6, Hs-CRP and PAI-1 activity were higher in Group 5 than all patients except for the anemic group and the TAC level was lower. When the data showing that morbidity and mortality were the most in the anemic group was evaluated together with the data that studied parameters of the anemic group was the closest to the wide Hg variable group, it can be said that it provides useful information for the explanation of the aforementioned mortality increase in this group. Although it may be argued that the possible cause of increased morbidity and mortality in this wide Hg variable group may be related to the variability of the recurrent tissue perfusion, its mechanism has not been fully explained. The results obtained in our study are the first data on this subject. Oxidative stress, inflammation and procoagulant activity associated with CVD and mortality are evident in this group, which seems to be a possible mechanism of increased mortality. In this sense, it is clear that the data we have obtained will contribute to the literature in the interest of understanding the mechanism of increased Hg fluctuation-mortality increase.

Conclusion

Oxidative stress, inflammation, and procoagulant activity markers were found to be high in the wide Hg variable group and the anemic group, while low in the Hg stable and anemic patients in the uremic patients with hemodialysis program. Oxidative stress, inflammation, and procoagulant activity associated with CVD and mortality seem to be the likely mechanism of increased mortality in groups with variable Hg course. This data is valuable for explaining one of the possible pathogenetic relationships; on the other hand, prospective studies with longer follow-up time are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Sumida K, Diskin CD, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, et al. Pre-End-Stage Renal Disease Hemoglobin Variability Predicts Post-End-Stage Renal Disease Mortality in Patients Transitioning to Dialysis. Am J Nephrol. 2017; 46(5): 397-407.
2. Mimura I, Tanaka T, Nangaku M. How the Target Hemoglobin of Renal Anemia Should Be. Nephron. 2015; 131(3): 202-9.
3. Chen Y, Fang W, Gu L, Cao L, Yan H, Huang J, et al. The role of hemoglobin variability as a prognostic indicator in peritoneal dialysis patients: a retrospective descriptive study. Int Urol Nephrol. 2018; 50(1): 167-71.
4. 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(11): 254-65.
5. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD, Collins AJ. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol. 2008; 3(1): 133-8.
6. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006; 17(4): 1181–91.
7. Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol. 2006; 1(6): 1205–10.
8. Lacson E Jr, Ofsthun N, Lazarus JM. Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis. 2003; 41(1): 111–24.
9. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol. 2008; 3(1):133–8.
10. Ishani A, Solid CA, Weinhandl ED, Gilbertson DT, Foley RN, Collins AJ: Association between number of months below K/DOQI haemoglobin target and risk of hospitalization and death. Nephrol Dial Transplant. 2008; 23(5): 1682–9.
11. Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI: Hemoglobin variability and mortality in ESRD. J Am Soc Nephrol. 2007; 18(12): 3164–70.
12. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int. 2005; 68(3): 1337–43.
13. Babior BM. The NADPH oxidase of endothelial cells. IUBMB Life. 2000; 50(4-5): 267–9.
14. Nguyen-Khoa T, Massy ZA, Pascal De Bandt J. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. Nephrol Dial Transplant. 2001; 16(2): 335–40.
15. Kato A, Odamaki M, Takita T. Association between interleukin-6 and carotid atherosclerosis in hemodialysis patients. Kidney Int. 2002; 61(3): 1143–52.
16. Stenvinkel P, Heimburger O, Jogestrand T. Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: association with Chlamydia pneumoniae seropositivity. Am J Kidney Dis. 2002; 39(2): 274–82.
17. Pecoits-Filho R, Bárány P, Lindholm B, Heimbürger O, Stenvinkel P. Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. Nephrol Dial Transplant. 2002; 17(9): 1684-8.

How to cite this article:
Kus T, Usalan ÖT, Usalan C. The relationship between hemoglobin variability and oxidative stress and inflammation in CKD. J Clin Anal Med 2019;10(1): 20-5.