The Relationship between Body Composition Analysis, Erythropoietin Requirements and Hemoglobin Variability in Hemodialysis Patients

Hemodiyaliz Hastalarında Hemoglobin Stabilitesi, Eritropoetin İhtiyacı ve Vücut Kompozisyon Analizi İlişkisi

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ABSTRACT

OBJECTIVE: Despite of similar body weight and body mass index patients might have different body composition. Our aim was to analyze the relationship between Hb variability, rHuEPO requirements and body composition analysis of MHD patients.

MATERIAL and METHODS: Monthly laboratory values and rHuEPO requirements of 110 MHD patients were collected. Patients were grouped according to Hb variability during last 6 months as Group LS (low stable, Hb<10 g/dL, n: 24), Group HS (high stable, Hb≥10 g/dL, n:43), Group V (variable, Hb varying between target, low target and high target levels, n:43).

RESULTS: Group LS had higher CRP but lower albumin levels compared to Group HS while Group V patients had lower albumin compared to HS and lower CRP levels compared to LS patients (p: 0.005). Group LS patients required significantly higher rHuEPO compared to other groups (p:0.0001). Group HS patients had significantly higher muscle mass (p:0.042) and muscle ratio (p:0.018) compared to Group LS.

CONCLUSION: Not only chronic inflammation but also nutritional status is closely related with Hb variability. We believe that there is a tendency to lose all body components in case of malnutrition associated with chronic inflammation while in malnutrition patients without chronic inflammation there is a tendency to loose mainly visceral fat component of total fat mass.

KEY WORDS: Body composition analysis, Erythropoietin requirements, Hemoglobin variability

ÖZ

AMAÇ: Benzer vücut ağırlığı ve vücut kitle indeksine sahip olmalarına rağmen hemodiyaliz hastaları yağ ve kas kitlesi gibi farklı vücut komponenti yüzdelerine sahip olabilirler. Biz bu çalışmada hemodiyaliz hastalarında hemoglobin değişkenliği, eritropoetin ihtiyacı (rHuEPO) ve vücut kompozisyon analizi arasındaki ilişkiyi saptamayı amaçladık.

GEREÇ ve YÖNTEMLER: 110 hemodiyaliz hastasının aylık laboratuvar değerleri ve rHuEPO ihtiyaçları kaydedildi. Hastalar son 6 aylık Hb değişkenliklerine göre 3 gruba ayrıldı; Grup LS (düşük stabil, Hb<10g/dL, n: 24), Grup HS (yüksek stabil, Hb≥10 g/dL, n:43) ve Group V (değişken, Hb değerleri hedef aralığın alt ve üst sınırları içinde değişen, n:43).

BULGULAR: Grup LS hastaları grup HS hastalarına göre daha yüksek CRP ve daha düşük albümin seviyelerine sahipken grup V hastaları grup HS hastalarına göre daha düşük albümin seviyelerine ve grup LS hastalarına göre daha düşük CRP seviyelerine sahiptirler (p: 0,005). Grup LS hastalarının rHuEPO ihtiyacı diğer iki gruba göre anlamlı derecede yüksekti (p:0,0001). Grup HS hastaları grup LS hastalarına göre daha yüksek kas kitlesi (p:0,042) ve kas oranına (p:0,018) sahiptiler. Group HS ve V hastaları grup LS hastalarına göre daha yüksek yağsız vücut kitlesine (p:0,047) sahiptiler.

SONUÇ: Kronik enflamasyon varlığı kadar hastaların nütrisyonel durumları da Hb değişkenliği varlığı ile sıkı ilişkilidir. Çalışma sonuçlarımıza göre, kronik inflamasyonla ilişkili malnütrisyonda tüm vücut komponentlerinde kayıp gözlenirken, kronik inflamasyon olmadan gelişen malnütrisyonda esas olarak visseral yağ kitlesinde kayıp gözlenir.

ANAHTAR SÖZCÜKLER: Vücut kompozisyon analizi, Eritropoetin ihtiyacı, Hemoglobin değişkenliği

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INTRODUCTION

Anemia has become a less significant problem in maintenance hemodialysis (MHD) patients with the clinical usage of erythropoiesis stimulating agents (ESA) since June 1989. The European Best Practice Guidelines (EBPG) for the management of anemia of end stage renal disease (ESRD) recommends a target range above 11 g/dL but not exceeding above 12-14 g/dL for hemoglobin (Hb) levels (1). With the publication of CREATE and CHOIR studies, both the upper and lower limits for target Hb concentration was lowered to 10-12 g/dL (2,3). Lower Hb levels are usually accepted as a risk factor for cardiovascular complications while on the other hand both using high doses of ESA and increasing Hb over target levels are also accepted as risk factors for hemoconcentration, thrombosis and cardiovascular mortality (4). While studying for optimal target Hb levels researchers observed that nearly all MHD patients experience Hb levels both above and below the target range during short follow-up periods. This condition which was called Hb variability gained more significance by the studies that report its relationship with increased mortality rates (5).

Multiple risk factors including chronic inflammation, hyperparathyroidism, iron deficiency, malnutrition, acute inflammatory conditions and infections, medications, hospitalization, dialysis modality and adequacy were found to be associated with Hb variability. Many of these clinical conditions are also main risk factors for ESA hyporesponsiveness, cardiovascular morbidity and mortality in MHD patients. Specifically malnutrition with or without chronic inflammation is a major risk factor decreasing patient survival (6). Some biochemical parameters including albumin, prealbumin, lipid profiles, ferritin levels, some clinical findings like anthropometric measurements and inquiries like subjective global assessment and mini nutritional assessment are widely used by clinicians for identifying malnutrition (7). Body composition analysis with the use of bioimpedance analyzers (BIA) is another method that could be used to assess nutritional status in MHD patients (8). However there is not enough data about the relationship between body composition, ESA responsiveness and Hb variability. We therefore aimed in this study to analyze the relationship between Hb variability with body composition analysis parameters in a group of MHD patients.

MATERIALS and METHODS

A total of 258 patients who were receiving MHD for three sessions per week were evaluated for inclusion. All MHD patients were receiving bicarbonate dialysis using a low flux synthetic dialyzer with an average blood flow of 300 to 350 mL/min with a Kt/V value during each treatment maintained at >1.2. Kt/V values were calculated monthly through predialysis and immediate postdialysis blood urea nitrogen levels by means of a single-compartment model of hemodialysis urea kinetics. Patients who had active infection, malignancy, been hospitalized in last 12 months were excluded. Patients who had a dry weight gain or loss greater than 3 kg in the last 6 months were excluded. Patients who had chronic inflammation (mean CRP level > 10 g/dL) were evaluated for presence of any malignancy, rheumatological disease or chronic infection before inclusion. After applying exclusion criterias 110 eligible patients were included (39 female, age; 53.8 ± 13.5 years). All patients received maintenance intravenous iron sucrose therapy in case of need. If ferritin level and transferrin saturation decreased to less than 100 ng/mL and 20%, respectively, 1g of iron sucrose was administered intravenously in divided doses over 10 consecutive hemodialysis sessions. Intravenous iron therapy was discontinued when the ferritin level and/or transferrin saturation increased to more than 800 ng/mL and 50%, respectively. rHuEPO (erythropoietin beta) dose was titrated monthly to maintain a target Hb level between 10 and 11 g/dL. rHuEPO requirements were collected for the last 6 months and calculated as U/kg/6 months. We retrospectively analyzed the prior 6 months' monthly laboratory values for albumin, C-reactive protein (CRP, normal levels; 0-5 mg/L), Hb, total cholesterol, LDL cholesterol and triglyceride and a mean value of each were recorded as the final data. Hematological and biochemical parameters were studied by standardized laboratory methods.

Body composition analyses were performed within 30 min after a clinically stable and euvolemic dialysis session. Body compositions were measured using the Tanita BC-420MA Body Composition Analyzer (Tanita, Tokyo, Japan). For the BIA measurements, the subject stood in an upright position with the bare feet on the analyzer footpads. The impedance between the 2 feet was measured while an alternating current (50 kHz and ~200 μA) passed through the lower body. Body weight, muscle, fat, and fat free mass, muscle ratio, fat ratio, visceral fat ratio values of each patient were measured and recorded. For analysis patients were grouped according to Hb variability during last 6 months as Group LS (low stable, All Hb values < 10g/dL, n: 24), Group HS (high stable, All Hb values ≥ 10 g/dL, n:43), and Group V (variable, Hb values varying between target, low target and high target levels, n:43).

Statistical analyses were performed by using the SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA). Normality of data was analyzed by using a Kolmogorov-Smirnov test. All numerical variables with normal distribution were expressed as the means ± standard deviations (SD), while variables with skew distribution were expressed as medians and interquartile range (IR). Categorical variables were expressed as percentages and compared by chi-square test. Normally distributed numeric variables were analyzed by independent samples t or One-Way ANOVA (Post-Hoc Tukey) tests. Skew distributed numeric variables were compared using the Mann-Whitney U and Kruskal Wallis tests. Spearman and Pearson Correlation tests were used for correlation anayses. A p-value < 0.05 was considered as statistically significant.

RESULTS

Patient groups were similar in means of demographic characteristics. Group LS had higher CRP levels but lower albumin levels compared to patients with Group HS (p: 0.005, Table I). On the other hand Group V patients had lower albumin compared to HS patients and lower CRP levels compared to LS patients (p: 0.005). Group V patients had similar CRP levels with HS and similar albumin levels with LS group patients. Group LS also had lower triglyceride levels compared to Group HS (p:0.014, Table I). Despite no statistical significance, there was a tendency for higher levels of total cholesterol and LDL cholesterol in Group HS compared to LS patients while Group V patients were in an intermediate position (p: 0.074, 0.06 respectively).

In means of body composition analysis, Group HS patients had significantly higher muscle mass (p:0.042, Table I) and muscle ratio (p:0.018, Table I) compared to Group LS. Group V patients also had significantly higher muscle ratio (p:0.02, Table I) compared to Group LS. Group HS and V patients had significantly higher fat free mass (p:0.047, Table I) than group LS patients. Group HS patients had significantly higher visceral fat ratio (p:0.004, Table I) compared to Group LS.

Table I: Comparison of study groups.

Mean ± SD Median (IR)	**Group LS (low stable, Hb < 10g/dL) n: 24**	**Group HS (high stable, Hb ≥ 10 g/dL) n: 43**	**Group V (variable Hb) n: 43**	**P value**
Gender (F/M)	12/12	10/33	17/26	0.07
Age (year)	49.3 ± 15.1	55.5 ± 12.8	54.7 ± 12.9	0.174
Etiology (n) Diabetes Mellitus Hypertension Polycystic disease Other Unknown	 - 4 9 2 9	 4 9 3 13 14	 6 6 2 22 7	 0.268
Duration of dialysis (year)	9.1 ± 6.2	10.1 ± 5.7	9.3 ± 5.2	0.709
CRP (mg/dL)	**14.3 (21.6)**	**8.8 (9.8)**	**6.8 (13.8)**	**0.005**
Albumin (g/dL)	**3.1 ± 0.4**	**3.9 ± 0.7**	**3.3 ± 0.4**	**0.001* 0.005****
Total cholesterol (mg/dL)	138.9 ± 33.2	158.4 ± 40.9	147.7 ± 26.7	0.074
LDL-cholesterol (mg/dL)	66.5 ± 26.5	82.3 ± 29.8	77.1 ± 20.5	0.06
Triglyceride (mg/dL)	**106 (52)**	**150 (129)**	**118 (92)**	**0.014*, 0.039*****
Body mass index (kg/m²) Dry weight change +/- (gr/6 months)	24.1 ± 4.9 + 450 gr	24.3 ± 4.5 + 580 gr	23.6 ± 5.4 - 540 gr	0.119 0.184
Fat mass (kg)	14.8 ± 12.7	16.4 ± 9.4	15.2 ± 10.2	0.814
Fat free mass (kg)	**42 (10)**	**49.3 (13.1)**	**47.6 (13.9)**	**0.047*, *****
Muscle mass (kg)	**40.1 ± 6.7**	**45.9 ± 8.3**	**44.2 ± 8.2**	**0.042***
Fat ratio (%)	21.3 ± 12.9	23.8 ± 10.1	23.3 ± 11.4	0.666
Muscle ratio (%)	**65.8 ± 9.1**	**72.2 ± 9.6**	**72.7 ± 10.8**	**0.018*, 0.02*****
Visceral fat ratio (%)	**5.7 ± 4.5**	**9.6 ± 4.6**	**7.8 ± 4.3**	**0.004***
Hemoglobin (g/dL)	**9.3 ± 0.7**	**11.7 ± 1**	**10.4 ± 0.7**	**0.0001**
rHuEPO (U/kg/6 months)	**4912.5 ± 1851.0**	**2031.6 ± 1853.4**	**3913.4 ± 1867.4**	**0.0001*,**, 0.093*****
Total IV iron (mg/6 months)	**1200 (1350)**	**1000 (1200)**	**800 (1000)**	**0.524**

* p value for comparison of Groups LS and HS, ** p value for comparison of Groups HS and V, *** p value for comparison of Groups LS and V

Group LS patients required significantly higher amounts of rHuEPO compared to both Group HS and V while Group HS had lowest rHuEPO needs and Group V been in the middle of other two groups (4912.5 ± 1851.0, 3913.4 ± 1867.4, 2031.6 ± 1853.4 U/kg/6 months, p: 0.0001, Table I).

Correlation analyses of study group revealed that total rHuEPO requirements were negatively correlated with muscle mass (r:-0.379) and visceral fat ratio (r:-0.214, p: 0.001, 0.025 respectively, Figures 1,2). Serum CRP levels were positively correlated with rHuEPO requirements (r: 0.208, p: 0.02).

DISCUSSION

Anemia is a well-known predictor of mortality in MHD patients. Although ESA have been used to treat anemia in these patients, optimal Hb targets remain unclear, and there are concerns about the safety of normal Hb levels as a target for ESA therapy. Recently the phenomenon of Hb variability has been considered as a factor that influences morbidity and mortality in MHD patients (9). Boudville et. al. demonstrated that the degree of Hb variability was greater in patients who were receiving ESA (10). In retrospective analyses, Yang et al. (5) reported that a greater Hb variability was associated with poor survival rates. With a large scaled retrospective study of 152846 patients, Ebben et al. (9) characterized six different types of Hb variability patterns and reported that consistently low Hb levels had the highest percentage of hospitalizations and the highest number of comorbid conditions. However some contradictory findings were also been reported recently. Gilbertson et al. (11) retrospectively analyzed 159720 MHD patients and reported that number of months with Hb values below the target range, rather than Hb variability itself, may be the primary driver of increased risk of death.

In our study group we observed that consistently low stable (Hb < 10 g/dL) in the last 12 months was significantly associated with chronic inflammation defined as increased CRP levels. Also we observed that rHuEPO requirements were positively correlated with serum CRP levels. Several studies have reported that markers of inflammation are associated with a decreased response to ESA treatment (12). Evidence suggests that inflammation is an important factor associated with Hb variability. Similarly, Kalantar Zadeh et al. reported a significant association between EPO hyporesponsiveness and inflammation (13). In another retrospective study of 225 hemodialysis patients, high CRP values were associated with less stable Hb levels (14). Similarly Barany et al. reported a significant correlation between Hb variability and CRP levels (15). Contradicting to these previous findings we observed that only low stable Hb group had higher CRP values but Hb variability group had similar CRP levels with high stable group. However we also observed a higher rHuEPO requirement in Hb variability group compared to high stable Hb group.

Albumin is a negative acute phase reactant but it is accepted as an important predictor of malnutrition and mortality in MHD population with other markers of malnutrition. In our study, Group V patients had lower CRP levels compared to Group LS, despite of similar albumin levels. Conversely despite of similar CRP levels group V patients had lower albumin levels compared to group HS patients (Table I). So we think that low albumin levels in these patients are not associated with inflammation

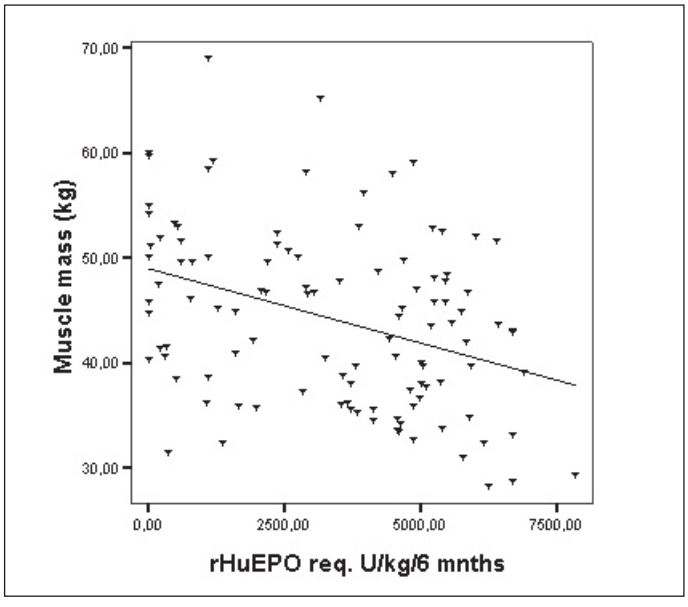

Figure 1: *Correlation analyses of study group revealed that total rHuEPO requirements were negatively correlated with muscle mass (r:-0.379, p: 0.001).*

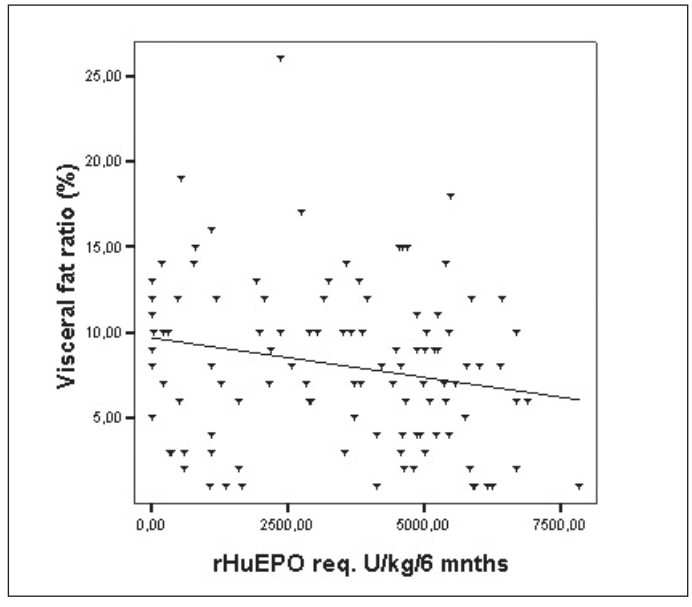

Figure 2: *Correlation analyses of study group revealed that total rHuEPO requirements were negatively correlated with visceral fat ratio (r:-0.214, p: 0.025).*

but associated with malnutrition. Supporting this hypothesis, these patients had poorer BIA findings compared to Group HS patients but better compared to Group LS. So we think that in patients with chronic inflammation and malnutrition rHuEPO hyporesponsiveness is more severe compared to patients with malnutrition alone. Clinically malnutrition associated with chronic inflammation is generally accepted as a wasting syndrome and it is harder to treat these patients without treating underlying inflammatory problems. However patients with malnutrition alone usually respond to nutritional support.

It has been reported that low BMI is correlated with poor survival outcomes in MHD patients in contrast to an otherwise healthy population. Although BMI is often used as an indicator of nutritional status, it is not an adequate indicator for body composition analysis because it does not differentiate skeletal muscle mass or body water from fat mass (16). Supporting these previous findings we also observed significantly different body compositions in Hb variability groups with similar BMI values. We observed LS patients had lowest muscle mass, and fat free mass, while Group V patients had intermediate values and HS patients had highest muscle and fat free mass values while all groups had similar BMI and fat mass values. We also observed that visceral fat ratio (source of short termed energy needs) was significantly lowest in Group LS, intermediately positioned in Group V and highest in Group HS patients (Table I). Interestingly, supporting our findings, Honda et al. observed that, high BMI patients with protein energy wasting (PEW) were characterized by increased fat body mass, low lean body mass and inflammation (17). In another study, high BMI and muscle mass were independently associated with greater survival even after extensive multivariate adjustment for available surrogates of nutritional status and inflammation (18). The fat free mass can serve as an index of muscle mass and somatic protein storage, whereas fat mass more directly reflects energy storage. Fat mass is also an important source of adipokines and proinflammatory cytokines, including interleukin 6 (IL-6), which is associated with decreased EPO sensitivity. Contradictory findings also could be found about increased EPO response in patients with higher fat mass. In a study by Axelsson et al. in which authors analyzed 166 ESRD patients and reported higher leptin levels in patients with higher fat mass and a negative correlation with leptin levels and EPO requirements (19). So we believe that malnutrition that is associated with muscle loss, with preserved or not preserved fat mass and chronic inflammation could lead to severe EPO hyporesponsiveness. Patients with malnutrition and muscle loss but without chronic inflammation seem to be in an intermediate zone of Hb variability and their EPO requirements tend to be high but not as high as the previous group. Patients who do not have any inflammatory status and have higher fat and muscle mass require significantly lower rHuEPO doses and have high stable Hb levels. Our findings therefore seem to support the "Fat is good but muscle is better" saying (20, 21).

In conclusion, we suggest not only chronic inflammation but also nutritional status is closely related with Hb variability and total rHuEPO requirements. We believe that there is a tendency to loose all component of body mass in case of malnutrition associated with chronic inflammation while in malnutrition patients without chronic inflammation there is a tendency to loose mainly the visceral fat component of total fat mass.

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