Is There Any Association Between Serum Iron And Copper Levels In Hemodialysis Patients?

Hemodiyaliz Hastalarında Bakır ve Demir Düzeyleri Arasında Herhangi Bir İlişki Varmıdır?

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Özet

Çalışmanın amacı, hemodiyaliz hastalarında serum demir (Fe), bakır (Cu) ve ferritin düzeylerindeki değişiklikleri tespit etmek ve ferritin düzeyleri ile elementler arasında bir ilişkinin olup olmadığını belirtmekti. Çalışmaya 2-16 yıldır diyalize giren (yaş ortalaması 50.26±16.36) 47 hemodiyaliz hastası (hemodiyaliz grubu) ve 23 sağlıklı kişi (yaş ortalaması 39.52±11.54) (kontrol grubu) dâhil edildi. Hemodiyaliz grubunda kan numuneleri diyaliz öncesi ve sonrası alındı. Veriler, gruplar arasında serum Fe düzeyleri bakımından önemli bir fark bulunmadığını gösterdi. Ancak, diyaliz öncesi Cu düzeyleri ve de diyaliz öncesi ve sonrası ferritin düzeyleri kontrol grubuna göre daha yüksekti (sırasıyla $p<0.05$, $p<0.001$). Diyaliz öncesi ferritin-Fe ($r= 0.373$, $p<0.05$) ve Fe-Cu ($r= 0.410$, $p<0.01$) düzeyleri arasında önemli pozitif korelasyon bulundu. Bu çalışmadan elde edilen bulgular, serum Cu düzeylerindeki değişikliklerin hemodiyaliz hastalarında önemli olabileceğini düşündürmektedir. Bununla birlikte, Cu ve Fe arasındaki korelasyon bu elementler arasında bir ilişkinin olduğunu göstermektedir. Fe ile Cu arasındaki ilişkinin aydınlanması için daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Hemodiyaliz, Demir, Ferritin, Bakır

Abstract

The aim of the present study was to determine changing in serum iron (Fe), copper (Cu) and ferritin levels in hemodialysis patients and to indicate whether there were any correlations between elements and ferritin levels. The study was carried out on 47 hemodialysis patient with the mean age 50.26±16.36 yr who were dialyzed with a range of 2-16 years. This group called as "Hemodialysis group". Blood samples were taken before (pre-hemodialysis) and after (post-hemodialysis) the hemodialysis session. "Control group" included 23 healthy volunteers with the mean age 39.52±11.54 yr. The findings demonstrated that there were no significant differences between the all groups according to data of serum Fe levels. However, serum Cu levels were higher in pre-hemodialysis than the control group ($p<0.05$) and serum ferritin levels were higher in group pre and post-hemodialysis than the control group ($p<0.001$). In pre-hemodialysis a significant positive correlations between ferritin and Fe ($r=0.373$, $p<0.05$), Fe and Cu ($r=0.410$, $p<0.01$) were determined. Findings obtained from the study deliberate that alterations in the levels of Cu may be important for the hemodialysis patients. In addition to correlation between Fe and Cu suggests that there is association between these elements. Further studies are necessary to clarify the association between Fe and Cu.

Key Words: Hemodialysis, Iron, Ferritin, Copper

Introduction

Although most research on uraemic toxicity has focused on retention or removal of organic solutes, subtle changes in concentration of inorganic compounds are also important because these compounds may have significant clinical consequences (1). Therefore, the levels of electrolytes must be kept in a rather narrow physiological range, otherwise life-threatening events may occur (2). On the basis of the results, the abnormal metabolism of trace metals contributes to a part of the uremic symptoms unresolved by maintenance hemodialysis (3).

Abnormalities of trace elements are primarily the result of uremia and may be further modified, and on the other hand may be sometimes greatly exacerbated by the dialysis procedure. To prevent some complications in chronic hemodialysis patients, it is too important to regulate the levels of trace elements by adequate water treatment (4).

Iron is important for hemoglobin formation and productive erytropoiesis. In hemodialysis patients, accurately assessing iron status is an essential for diagnosing iron defiency, monitoring the response to iron supplementation, and maintaining effective erythropoiesis (5). Besides, it is concluded that low baseline serum iron indicators are associated with increased mortality and hospitilazation in maintenance hemodialysis patients independent of hemoglobin levels, erythropoietin (EPO) and iron doses, indicators of nutrition and inflamation and comorbid conditions (6).

Serum ferritin level is both a marker of iron status and behaves as an acute-phase reactant and an indicator of inflammation and/or malnutrition in maintenance dialysis patients (7).

Copper is an element which plays an important role in biological systems as compenents of protein, enzymes and antioxidants (8).

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Table 1. The levels of parameters in control and patients group before dialysis (pre-hemodialysis) and after dialysis (post-hemodialysis)

Parameters	GROUPS			P VALUES		
	Control Group (A)	Pre-hemodialysis (B)	Post-hemodialysis (C)	A vs B	A vs C	B vs C
Ferritin(ng/ml)	86.15±14.33	631.74±67.18	767.77±84.64	0.000**	0.000**	0.285
Cu (µg/dl)	108±4.72	129±5.3	116±6.5	0.018*	0.229	0.322
Fe (µg/dl)	195±24.73	183±19	192±12	0.283	0.685	0.121

Data were expressed as mean ± SE
* P≤0.05
** P≤0.001

Much of the Cu in the plasma (60-95%) is bound to ceruloplasmin, in the erytrocytes (60%) is bound to SOD (superoxide dismutase)(4). Cu deficiency may lead to leukopenia-anemia, arterial aneurysms, cardiac arrhythmias, hypercholesterolemia, diarrhoea, and impaired utilization of iron, abnormal synthesis of collagen and elastin, myocardial necrosis, and enhanced cholesterol synthesis, atrophy of intestinal mucosa (9). Kirschbaum (7) conclude that there is relation between Cu and iron metabolism and the abnormalities in Cu metabolism and their influence on iron handling in renal failure are complex, and besides the researchers suggest that altered copper-ceruloplasmin function may contribute to abnormal iron management in the renal failure population (7).

Therefore, present study was undertaken to evaluate how serum iron (Fe), copper (Cu) and ferritin levels changed in hemodialysis patients, and whether there were any differences between healthy people and hemodialysis patients, and whether there were any correlations between these elements and ferritin levels.

Materials And Methods

Patients: Study was materialized with the 2001/130 numbered approvals and financial support of the Committee of Selcuk University of Scientific Research Projects Coordination Department. Present study involved 47 hemodialysis patients (34 female, 13 male), who were treated in Polyclinic of Hemodialysis in Department of Nephrology of Medical Faculty of Selcuk University. The mean ages of the patients were 50.26±16.36 yr. All patients were dialyzed three times a week and each session was at least 4 hour. They were dialyzed with polysulfone dialyzing membrane. The duration of dialysis range was 2-16 yr. Those patients who had hepatitis B, acute medical events, were using Al-containing drugs, were excluded in this study. This group called as "Hemodialysis Group".

"Control Group" was composed of 23 healthy volunteers (7 female, 16 male) with the mean age 39.52±11.54 yr. Those people had no any medical problem, were not using alcohol and were not smokers.

Samples Collection: The blood samples were taken from the hemodialysis patients in their regular monthly check-up. No extra blood samples were taken from the patients for those biochemical parameters that were mentioned for this study. The blood samples were used from remains of their check-up sample. Samples were collected immediately before (pre-hemodialysis) and after the dialysis (post-hemodialysis) sessions. Blood samples were not randomly collected.

Samples of control group were taken after 10 hour fasting. Control group was selected from the people who were doing their ordinary check-up. For those biochemical parameters analyzing, the samples were used from remains of their check-up blood samples, extra blood samples were not taken.

Serum ferritin levels were determined in Immulite 2000 auto analyzer (BIODPC, Diagnostic Products Corporation 5700 West 96th Street Los Angeles, CA 90045-5597, USA) by using Immulite test kit (catalog no: L2KFE2). Serum Fe and Cu levels were analyzed by inductively coupled plasma emission spectrometry (ICP-AES, Varian Australia Pty Ltd, Australia).

Statistical Analysis: Data were expressed as mean ± SE and analyzed with SPSS packet program. Student's t-test and Mann-Whitney U test were used to compare the groups. The levels of statistical significant were set at $p<0.05$, and $p<0.001$. Pearson Correlation coefficients were applied to evaluate the relationship between levels of trace elements and the other parameters and were set at $p<0.05$ and $p<0.01$ significances.

Results

Data concerning to hemodialysis group pre- and post-levels and control group have been shown in (Table 1).

In hemodialysis patients before hemodialysis session, the levels of Cu are higher than the levels of control group ($p<0.05$). There were no significant differences between the groups of post- and pre-hemodialysis, but post-hemodialysis levels were lower than the pre-hemodialysis.

There were no significant differences between levels of control's and hemodialysis patients' in evaluation of Fe levels. The highest levels were determined in control group.

The highest levels of ferritin were in post-hemodialysis group and these levels were significantly different from the control group ($p<0.001$) but were not different from the pre-dialysis's levels. Besides pre-hemodialysis patients showed high levels of ferritin according to the levels of control group ($p<0.001$).

In hemodialysis patients before hemodialysis session, a positive correlation between ferritin and Fe ($r=0.373$ $p<0.05$), Cu and Fe ($r=0.410$, $p<0.01$) were determined. In control group and post-hemodialysis group, all the other correlations were not statistically significant (data were not shown in table).

Disscussion

It is well known that the concentrations of trace elements in biological tissues and fluids are important in health of the human beings. The concentration of several trace elements in end-stage renal failure patients is disturbed, and some of the trace metals may share pathway of absorption, distribution and accumulation. On the other hand, their presence is essential to the functions of enzyme cofactors, of structural and non-enzymatic proteins (10).

Deficiency or excessive of trace elements that effecting several diseases' diagnosis and prognosis have been also analyzing in hemodialysis patients. Lin et al. (11) and Krachler et al. (12) found important differences between the group of pre and post-hemodialysis according to data of plasma Cu levels. The highest levels of Cu were in group of post-hemodialysis. Moreover, Krachler et al. (12) concluded that plasma Cu levels distinctly and steadily increased during the hemodialysis treatment. Approximately 25% higher Cu concentrations were found at the end of the dialysis session. Concentrations of Cu in dialysis liquid do not markedly contribute to an increase of the Cu burden in dialysis patients because of the binding of 90-95% of copper to metalloproteins, which can not be dialyzed from the plasma to the dialysis liquid (12). Our data are not similar with the result of Lin et al. (11) and Krachler et al. (12).

In our study the patients have not clear abnormalities in Cu metabolism because their Cu levels were in normal range of references for healthy people. Seen from this aspect, we are in agreement with Krachler et al. (12) who determined that their patients have Cu levels in the normal range of references for healthy subjects. When we compared the levels of Cu in pre-and post hemodialysis group, we determined that post hemodialysis group had lower Cu levels but these differences were not statistically significant. In this connection, we considered that hemodialysis session did not make clear alterations in Cu levels.

However, Lin et al. (11) concluded that Cu levels were higher in prehemodialysis that control group. Our data are similar with these results. The researchers suggested that the levels of trace elements were altered by hemodialysis which might increase patient susceptibility to lipid peroxidation in uremia. In our research (13), the antioxidant and oxidant system has been studied in hemodialysis patients. So that, we are also in agreement with Lin et al (11) in evaluating the lipid peroxidation status. Pre-hemodialysis patients, the levels of MDA (Malondialdehyde), SOD ($p<0.001$) were higher and reduced form of GSH (glutathione) levels ($p<0.001$) were lower than levels of control's. MDA and SOD levels were higher in patients after hemodialysis than those in control group ($p<0.001$) in the study (13). According to results of antioxidant and oxidant levels in control and pre-hemodialysis, finding of decreased reduced form of GSH levels, increased MDA and SOD levels in prehemodialysis can take into consideration. We suggested that HD patients were subjected to oxidative stress, as indicated by increased lipid peroxidation and reduced antioxidant levels. However, estimating the levels of SOD, GSH and MDA in pre- and post-hemodialysis patients, it seems the relations of SOD and MDA in hemodialysis patients after and before dialysis session must be investigate more extent to clarify the changing in oxidant/antioxidant defense system during the dialysis session.

It may be concluded that alterations of Cu levels are the result of lost of factors. Oxidant- antioxidant system's alterations are important and one of the factors that can affect Cu levels.

Meanwhile, Hsu et al. (3) hypothesized that the aging process with altered gastrointestinal absorption, more so than hemodialysis itself, contributed to zinc deficiency and copper accumulation in hemodialysis patients.

On the other hand, whole blood Cu levels did not demonstrate significant alterations between hemodialysis patients and healthy people but erythrocyte Cu levels were significantly higher in healthy people (8). Our data are not similar with these results. The researchers used cuprophane dialysis membrane in their study, so these differences can be attributed to using different dialysis membrane.

Iron deficiency, infection/inflamation and bleeding are common during anemia. Iron deficiency is especially problematic because it is prevalent, increases the severity of anemia and reduces the ability of the patient to respond to treatment (14). The vast majority of patients respond very well to treatment, but 5-10% of patients show some resistance to erythropoietin, the most common cause of which is iron deficiency. The targets of hemoglobin concentration in predialysis patients are object of continuous re-examinations (15). Our findings concerning to Fe levels in all groups, are consistent with the result of Löcsey at al. (9). The researchers determined that the iron levels were lower in hemodialysis group than the control group but were not statistically important.

They suggested that the serum concentrations of iron increased with the frequency of hemodialysis treatments and with the duration of the dialysis range. In this connection, it can be said that the iron metabolism may be changed according to several factors in hemodialysis, so it is important to reveal a study which can be performed on the relations between the iron levels and duration of the different dialysis membranes, the frequency of dialysis treatments.

As it is known, serum ferritin concentrations and iron saturation ratio are among the two most commonly used markers of iron status in maintenance dialysis patients. Besides, it is indicated that serum ferritin is a marker of iron store independent of its range but correlates with inflamation only in a restricted range of 200-2000 ng/ml in maintenance hemodialysis patients (6).

In the present study we determined significant differences between the groups of pre-and post-hemodialysis and control group. Hemodialysis patients demonstrated high levels of ferritin than the healthy subjects. Besides, post hemodialysis patients had higher levels than pre-hemodialysis patients'. But, the differences were not significantly important.

In evalution the correlation between the ferritin and elements, we determined that healthy subjects and post-hemodialysis patients did not demonstrate any significant correlation between ferritin-Cu, ferritin-Fe and Cu-Fe levels. In pre-hemodialysis group, a significant correlation between Fe-Ferritin (r=0.373) and Fe-Cu (r=0.410) levels were determined. Therefore, we can say that there are associations between iron levels and ferritin, Cu levels in hemodialysis patients before the dialysis session.

On the basis of above results, present study is important in determining the relations through ferritin, Cu and Fe levels in role of acceptable treatment of hemodialysis but not enough to clarify the effects of the elements and ferritin and their relations in hemodialysis patients. Our findings that show that levels of Cu are statistically different in groups and relationship between Cu and Fe levels, suggest that it may be important to analyze copper levels in hemodialysis patients as a routine control. However, further studies with a more number of patients, which perform on comparing the different dialysis membrane, involving the groups who have different frequency of hemodialysis treatments and different the duration of the dialysis range, are necessary. As it is known, nowadays, studies are different from each other in about alterations of levels of elements in hemodialysis patients.

These differences can be attributed to variation of subjects' criteria, which included to the study (number of subjects, duration of dialysis range), of times of blood samples collections and especially of dialysis membrane. According to this variations, finding different results are natural, however are not enough to clarify the effects of elements in hemodialysis patients during their treatments.

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