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The relationship between dialysis adequacy and the rate of change in uric acid level by hemodialysis

Hemodiyaliz ile ürik asit düzeyindeki değişim oranı ile diyaliz yeterliliği arasındaki ilişki

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Abstract

Aim: Although one of the commonly used methods for determining dialysis adequacy is the urea kinetic model, it is not the gold standard. Different parameters are needed to determine dialysis adequacy. In our study, we investigated the relationship between urea reduction rate (URR) and Kt/V which are used to assess dialysis adequacy and the rate of change in uric acid, a purine metabolite, by hemodialysis.

Methods: A total of 133 patients who had undergone hemodialysis treatment due to renal failure between March 2010 and September 2010 were evaluated retrospectively. Urea kinetic modeling was used to measure dialysis adequacy. The following formula was used to do this; Kt/V=-ln(R-0.008xT)+(4-3.5xR)xUF/W[R; postdialysis blood ureanitrogen (BUN)/predialysis BUN, T; duration of dialysis (hr), UF; total ultrafiltration during dialysis (L), W; patient weight after dialysis (kg)]. The urea reduction rate was calculated using the formula; URR(%)=100x(1-postdialysis BUN/predialysis BUN). Uric acid reduction rate (UARR) was calculated using the formula; UARR(%)=100x(1-Uric acid after/Uric acid before). The relationship between URR and Kt/V ratios which are used to assess dialysis adequacy and UARR is evaluated.

Results: Median urea, uric acid and creatinine reduction rates were 72%, 74% and 63.9%, respectively. There was a statistically significant correlation between reduction rates of uric acid, creatinine and urea after dialysis ($p<0.001$). There was a statistically significant relationship between URR and Kt/V which are used to assess dialysis adequacy,and UARR ($p<0,001$). According to the ROC analysis in our study, we defined UARR value that will demonstrate dialysis adequacy as at least 65.8% (sensitivity 97.9% and specificity 82.6%, area under the ROC curve=0.880, $p<0.001$).

Conclusion: A significant relationship was found between the URR and Kt/V ratios which are used to assess dialysis adequacy and UARR. We also determined in our study that the UARR value that shows dialysis adequacy should be at least 65.8%. To our knowledge, this is the first study to evaluate the relationship between UARR and dialysis adequacy. However, thefindings need to be confirmed by large, prospective, clinical trials.

Keywords: Dialysis adequacy, Urea kinetic model, Kt/V, Uric acid

Öz

Amaç: Diyaliz yeterliliğini belirlemede sık kullanılan yöntemlerden biri üre kinetik modelleme olmasına rağmen altın standart değildir. Diyaliz yeterliliğinin belirlenmesinde farklı parametrelere ihtiyaç vardır. Biz çalışmamızda bir pürin metaboliti olan ürik asitin hemodiyaliz ile değişim oranına bakarak diyaliz yeterliliğini değerlendirmede kullanılan üre azalma oranı (URR) ve KT/V ile arasındaki ilişkiyi araştırdık.

Yöntemler: Çalışmamızda 2 merkezde Mart 2010 ile Eylül 2010 tarihleri arasında böbrek yetmezliği nedeniyle hemodiyaliz tedavisi gören toplam 133 hasta retrospektif olarak değerlendirildi. Diyaliz yeterliliğini ortaya koymak için üre kinetik modelleme kullanıldı. Bunun için Kt/V=–ln(R–0.008xt)+(4– 3.5xR)xUF/W([R=diyaliz sonrası kan üre azotu (BUN) / diyaliz öncesi BUN, t= diyaliz seansının süresi (saat), UF= diyalizde yapılan toplam ultrafiltrasyon (L), W= diyaliz sonrası hasta ağırlığı (kg)] formülü kullanıldı. ÜRR(%) = 100 x (1- BUNsonra / BUNönce) formülü kullanıldı. Ürik asit azalma oranı (UARR) (%) = 100 x (1- Ürik asit sonra / Ürik asit önce) formülü ile hesaplandı. UARR ile diyaliz yeterliliğini değerlendirmede kullanılan URR ve Kt/V oranları arasındaki ilişki değerlendirildi.

Bulgular: Ortanca üre, ürik asit ve kreatinin azalma oranı sırası ile %72, %74, %63,9 olarak bulundu. Ürik asit, kreatinin ve ürenin diyaliz ile azalma oranları arasında istatistiksel olarak anlamlı korelasyon saptandı ($p<0,001$). UARR ile diyaliz yeterliliğini değerlendirmede kullanılan Kt/V ve URR arasında istatistiksel olarak anlamlı ilişki bulunmuştur ($p<0,001$). Çalışmamızda, ROC analizine göre, diyaliz yeterliliğini gösterecek UARR değerinin en az %65,8 (duyarlılık %97,9, özgüllük %82,6, ROC eğrisinin altındaki alan =0,880, $p<0,001$) olarak belirledik.

Sonuç: UARR ile diyaliz yeterliliğini değerlendirmede kullanılan URR ve Kt/V oranları arasında istatistiksel açıdan anlamlı ilişki tespit edildi. Ayrıca çalışmamızda diyaliz yeterliliğini gösterecek UARR değerinin en az %65,8 olması gerektiğini belirledik. Bizim bilgimize göre bu çalışma UARR ile diyaliz yeterliliği arasındaki ilişkiyi değerlendiren ilk çalışmadır. Fakat bu bulgunun büyük, prospektif, klinik çalışmalar ile teyit edilmeye ihtiyacı vardır.

Anahtar kelimeler: Diyaliz yeterliliği, Üre kinetik model, Kt/V, Ürik asit

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Introduction

Chronic renal disease is a pathophysiologic process that results in reduction in nephron counts and nephronic functions and frequently progresses to end-stage renal failure resulted from many etiologic causes [1]. Patients with end-stage renal disease (ESRD) should be given one of the renal replacement therapies. Renal replacement treatments are hemodialysis, peritoneal dialysis, and kidney transplantation. As the kidney failure progresses, the serum concentration of many organic and inorganic substances, called uremic toxins, increases [2].

Despite the treatment of ESRD or uremic syndrome by dialysis, uremic toxins have not yet been fully understood. Uremic syndrome is the result of abnormal accumulation of various substances that inhibit physiological and biochemical functions in the body [2,3]. The size of these accumulating substances can vary from less than 300 daltons (such as urea) to 12000 daltons (such as medium-sized molecules, beta2 microglobin, myoglobin). The importance of each of the uremic toxin groups is still unclear.

Uric acid, xanthine, hypoxanthine, and guanosine are the most important purine metabolites that accumulate in the uremia. The purine metabolites that constitute the major class of uremic toxins cause impairment of calcitriol and vitamin D metabolism [3-6]. These metabolites play a role in the immunodeficiency seen in hemodialysis patients [7]. They were also found to be associated with loss of appetite and weight loss seen in patients with ESRD [8]. For this reason, it is important that uric acid and other purine metabolites are efficiently removed from blood by dialysis.

The purpose of this study is to investigate the relationship between the rate of reduction in uric acid levels and dialysis adequacy in patients undergoing hemodialysis due to renal insufficiency.

Materials and methods

In our study, a total of 133 patients who had undergone hemodialysis treatment due to renal insufficiency between March 2010 and September 2010 were evaluated retrospectively in two hemodialysis centers.

Inclusion criteria:

1. Patients undergoing hemodialysis treatment due to renal insufficiency

2. Patients informed about the study and accepted to participate

A total of 133 patients were enrolled. Patients' age, gender, medications, height and weight were recorded.

Blood samples were taken from patients after 12 hours of fasting from the needle attached to the artery before starting dialysis and receiving serum and heparin for biochemical parameters (glucose, creatinine, BUN, total cholesterol, LDL cholesterol, uric acid, sodium, potassium, calcium, phosphorus, albumin, hemogram). After hemodialysis, the blood pump rate of the instrument was reduced to 50ml/min for 15 seconds and blood sample was taken for uric acid, creatinine, and urea at the end of this period; then the dialysis procedure was terminated.

Uric acid was measured in Synchron LX20 autoanalyzer using the Syneron System Uric Acid Assay kit with enzymatic trinder method. Urea kinetic modeling was performed to demonstrate dialysis adequacy. The following formula was used to do this; Kt/V=-ln(R-0.008xT)+(4-3.5xR)xUF/W [R; postdialysis blood ureanitrogen (BUN)/predialysis BUN, T; duration of dialysis (hr), UF; total ultrafiltration during dialysis (L), W; patient weight after dialysis (kg)]. The urea reduction rate was calculated using the formula; URR(%)=100x(1-postdialysis BUN/predialysis BUN). Uric acid reduction rate (UARR) was calculated using the formula; UARR(%)=100x(1-Uric acid after/Uric acid before).

Statistical Analysis: Data analysis was done in SPSS 11.5 for Windows software package. The Shapiro-Wilk test was used to determine whether the distribution of continuous variables was close to normal. Descriptive statistics for continuous variables were expressed as mean, standard deviation, median, minimum, maximum while categorical variables were expressed as the number of cases and (%). Wilcoxon Signed test was used to assess whether statistically significant changes were observed in the input and output laboratory measurements. Spearman's correlation test was used to examine whether there was any significant correlation between continuous variables. P values of less than 0.05 ($p<0.05$) were regarded as statistically significant.

Results

Forty eight of 133 patients were female (36.1%) and 85 were male (63.9%). Median age of the patients included in the study was 60 years. The average time at which patients started dialysis is 43.5 months. All patients were dialyzed three times a week for 4 hours with bicarbonate dialysis solution using dialysers with a blood flow rate of 300 ml/min and dialysate flow rate of 500 ml/min and a surface area of 1.5 m2. 129 of the patients were dialyzed with AV fistula (97%) and 4 with subclavian catheter (3%). The etiologic causes of renal failure were determined as hypertension in 55 (41.4%), diabetic nephropathy in 32 (24.1%), glomerulonephritis in 10 (7.5%), stone disease in 5 (3.8%), VUR in 6 (4.5%), idiopathic in 4 (3%), PKD (polycystic kidney disease)in 20 (15%) and multiple myeloma in 1 (0.8%) of the patients. Hepatitis B infection was detected in 5 (3.8%) of the patients and hepatitis C infection was detected in 10 (7.5%) of the patients. 118 (88.7%) patients did not have any hepatitis infection (Table 1).

In our study, a statistically significant positive correlation was found between the uric acid reduction rate and Kt/V ($p <0.001$), URR ($p <0.001$). There was no statistically significant correlation between uric acid reduction rate and laboratory parameters such as albumin, hemoglobin, protein, calcium, phosphorus.

The mean urea, creatinine and uric acid levels of the patients before and after dialysis were 138.6/40.5 mg/dl, 8.2/3 mg/dl and 6.1/1.6 mg/dl, respectively and a statistically significant reduction was detected ($p<0.001$) (Table 2 and Figure 1-3). Median urea, uric acid and creatinine reduction rates were 72%, 74% and 63.9%, respectively (Table 3).

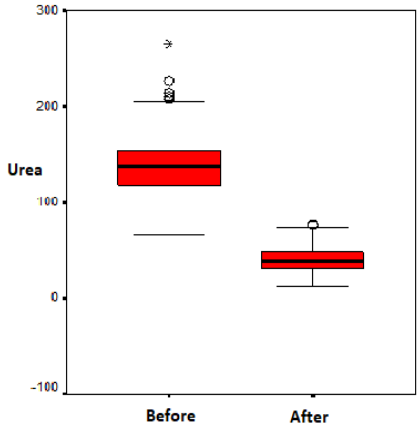

Figure 1: Urea levels of the patients before and after dialysis

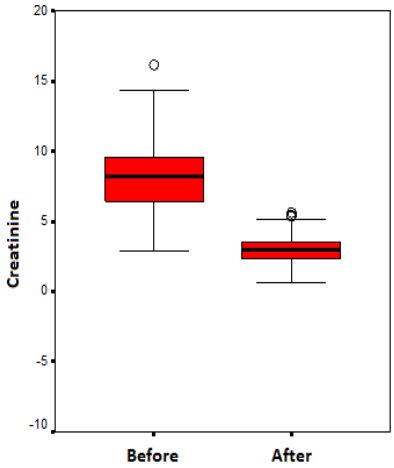

Figure 2: Creatinine levels of the patients before and after dialysis

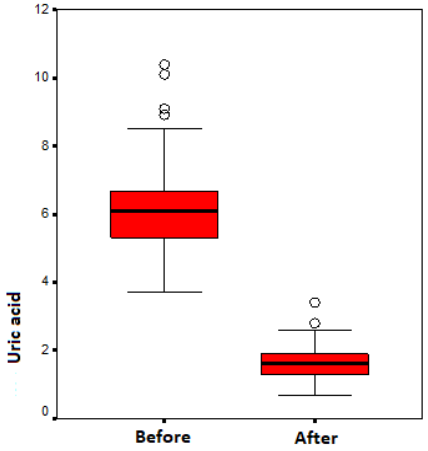

Figure 3: Uric acid levels of the patients before and after dialysis

Explanation for Figure 1-2-3: The horizontal line in the middle of each box shows the median value (50th percentile), while the lower and upper lines in the boxes show 25th and 75th percentiles, respectively. The lines in the lower and upper parts of the boxes show the minimum and maximum values, respectively. Circles indicate outliers, while stars indicate subjects with extreme values.

According to The European Best Practice Guidelines, single-pool Kt/Vurea is accepted as at least 1.4 (9). According to the urea kinetic model in our study, we considered Kt/V 1.4 and above as adequate dialysis. When ROC analysis was performed for dialysis adequacy, we determined the lower limit for UARR as 65.8% (sensitivity 97.9% and specificity 82.6%, area under the ROC curve = 0.880, p<0.001) (Figure 4).

Table 1: Demographic and Clinical Features Descriptive Statistics

Variables	n	%
Gender		
Female	48	36.1
Male	85	63.9
Vascular access		
AVfistula	129	97.0
Subclavian	4	3.0
Flow rate(ml/min)		
300	133	100.0
Hemodialysis duration (minutes)		
240	133	100.0
Hemodialysis Frequency (weeks)		
3	133	100.0
Etiology		
Hypertension	55	41.4
Diabetes Mellitus	32	24.1
Glomerulonephritis	10	7.5
Nephrolithiasis	5	3.8
Vesicoureteral reflux	6	4.5
İdiopathic	4	3.0
Polycystic kidney disease	20	15.0
Multiple myeloma	1	0.8
HEPATIT STATUS		
No hepatitis	118	88.7
HBV +	5	3.8
HCV +	10	7.5
Total	133	100.0

Tablo 2: Laboratory values before and after dialysis

Variables	Mean	SD	Median	Minimum	Maximum	p
Urea						<0.001
Before	138.6	32.82	138.0	65.0	265.0	
After	40.5	13.15	38.0	11.0	77.0	
Creatine						<0.001
Before	8.2	2.32	8.2	2.8	16.1	
After	3.0	0.98	2.9	0.6	5.6	
Uric acid						<0.001
Before	6.1	1.18	6.1	3.7	10.4	
After	1.6	0.46	1.6	0.7	3.4	

Table 3: Descriptive Statistics for Kt / V, URR, Uric Acid and Creatinine Reduction Rates

Variables	Mean	SD	Median	Minimum	Maximum
KTV	1.3	0.14	1.4	0.9	1.7
UARR(%)	73.3	6.18	74	53.5	88.3
Creatinine reduced rate (%)	63.7	6.15	63.9	42.6	84.3

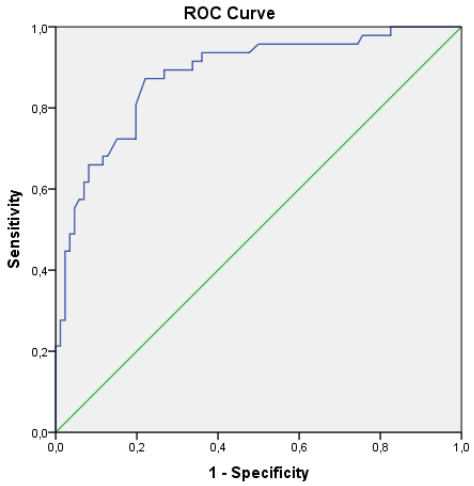

Figure 4: The predictive value of UARR for dialysis adequacy (sensitivity 97.9% and specificity 82.6%, area under the ROC curve = 0.880), p <0.001.

Discussion

Hemodialysis is the most commonly applied renal replacement method in Turkey and in the world. Despite the use of modern techniques, the average life span in hemodialysis patients is reported to be even shorter than those with malignant disease [10].

Urea is the most commonly used substance in clinically determining the clearance of small molecules. Nonetheless, the kinetic behavior of urea does not represent that of water-soluble small molecular weight uremic toxins [11]. Uric acid, xanthine, hypoxanthine and guanosine are the most important purine metabolites that accumulate in uremia. The major purine metabolites of uremic toxins were found to be associated with impaired calcitriol and vitamin D metabolism, immunodeficiency, loss of appetite and weight loss [3-8]. Hyperuricemia has also been associated with hypertension, heart failure, and atherosclerosis [12-14]. Therefore, effective removal of uric acid is important.

In a study by Vanholder and colleagues [15] on uremic toxins before and after hemodialysis, they found the highest rate of reduction after dialysis to be 66% for uric acid and hydroxyhippuric acid. In the same study, they found that the change rate of urea by dialysis as 60% and that of creatinine as 55%. In the same study, a high degree of correlation was found

between changes in uric acid, creatinine, and urea concentration. The reduction rates of urea (UR), creatinine (CR) and uric acid (UA) were found to be 73.8%, 69.5% and 75.1%, respectively, in a study conducted by De Smet et al [17] and the rate of reduction in UR, CR and UA were significantly correlated [16]. In a study by Ricardo and his colleagues, the rates of clearance of urea, creatinine, and uric acid were found to be correlated at every minute of dialysis.

In a study by Carlo and colleagues [18] in which they compared the removal of uremic toxins in a group dialyzed with standard 4-hour bicarbonate dialysate with a group dialyzed with 8-hour low-bicarbonate dialysate, the reduction rates of UR, CR, and UA were found to be 69.3%, 62.7%, 75.8% in 4-hour dialyzed group, respectively and 74.6%, 65.9%, 79.9% in 8-hour dialyzed group. There was also a statistically significant correlation between reduction rates of UR, CR, and UA in both groups. In our study, the rates of reduction in median UR, CR and UA were found to be 72%, 63.9% and 74%, respectively. There was a significant correlation between the reduction rates of uric acid, creatinine and urea in our study ($p < 0.001$). These findings were consistent with some previous studies [16-18]. In our study, a statistically significant relationship was found between UARR and Kt/V, URR. We also determined that UARR value that demonstrates dialysis adequacy should be less than 65.8% according to ROC analysis in our study. To our knowledge, this is the first study to evaluate the relationship between UARR and dialysis adequacy determined by urea-kinetic models. We suggest that UARR can be used to determine dialysis adequacy similar to URR.

Kt/V is influenced by many factors such as daily protein uptake, lack of consideration of postdialysis urea rebound, and residual renal function [19]. For this reason, despite giving valuable information about dialysis adequacy of patients, it is not acceptable as a gold standard. Therefore, methods and parameters other than Kt/V should be evaluated for determination of dialysis adequacy.

The limitation of this study is that postdialysis plasma levels of uric acid may be affected by various conditions. In some studies, plasma uric acid levels were higher than normal after hemodialysis. This is explained by ischemic events occurring during dialysis [20,21]. Ischemic events that occur during dialysis increase the hydrolysis of adenosine triphosphate, anaerobic glycolysis, proteolytic conversion ofxanthine dehydrogenase into xanthine oxidase, and degradation of adenine nucleotides [20,21]. All these mechanisms result in the breakdown of adenosine triphosphate and the increase in uric acid during ischemia. One of the most prominent ischemic events that occur during dialysis in patients with ESRD is intradialytic hypotension [22]. Studies by Shinzato and colleagues [22] assessing plasma levels of purine nucleotides in patients with intradialytic hypotension during hemodialysis have shown an increase in purine metabolite during hypotension. In this study, purine metabolites at the end of dialysis were found to be lower than before dialysis. However, in the same study, there was a marked decrease in purine metabolites after dialysis in the group where hypotension was prevented in comparison to the group where intradialytic hypotension was developed during dialysis. In our study, it was not taken into account whether hypotension developed during dialysis. In addition, other factors which may affect plasma uric acid levels after dialysis, such as use of diuretics, hypothyroidism, obesity, diabetes mellitus, are not excluded. Another limitation of our study is that it has been done retrospectively with a small number of patients. This may limit the generalization of the results.

As a result; a statistically significant relationship was found between the URR and Kt/V ratios which are used to assess dialysis adequacy and UARR. We also determined in our study that the UARR value that indicates the dialysis adequacy should be at least 65.8%. To our knowledge, this is the first study to evaluate the relationship between UARR and dialysis adequacy. We suggest that the rate of change in uric acid levels before and after dialysis may be used to evaluate dialysis adequacy. However, it needs to be confirmed by large, prospective, clinical trials.

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