



Relationship between the level of uric acid and peritonitis in peritoneal dialysis patients; a retrospective cohort study

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ABSTRACT

Introduction: Peritonitis is a cause of mortality among peritoneal dialysis (PD) patients. Some studies suggested that uric acid (UC) levels may be effective in inflammatory processes. **Objectives:** We have examined the relationship between serum UC and peritonitis in PD patients.

Patients and Methods: A retrospective cohort study was conducted over six years.

The statistical population was all PD patients who underwent PD for at least six months. The sample size included 151 patients based on serum UC levels (less than or equal to 6.5 mg/dL, more than 6.5 mg/dL) and was divided into two groups. Both groups were compared using inflammatory factors and peritonitis.

Results: In total, around 100 patients (66.2%) had UC levels ≤ 6.5 mg/dL, and 51 patients (33.7%) had serum UC levels > 6.5 mg/dL. Peritonitis was observed in 72 (47.6%) patients. The frequency of peritonitis in the patients with greater levels of serum UC (51%) was higher compared to the other group (46%), but this difference was not statistically significant ($P=0.56$). The average hemoglobin level was lower in higher serum UC levels group ($P=0.002$). The mean levels of serum albumin ($P=0.002$), phosphorus ($P=0.004$), and creatinine ($P=0.02$) were lower in the group with serum UC below 6.5 mg/dL group.

Conclusion: There was no correlation discovered between peritonitis and serum UC levels. However, it seems that serum UC can serve as a marker among PD patients to predict the occurrence of anemia and malnutrition.

Implication for health policy/practice/research/medical education:

Our study used cheap and available serum uric acid index to predict the essential complications of peritonitis and anemia among peritoneal dialysis (PD) patients.

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Introduction

Chronic kidney disease is a growing disease worldwide, and the need for renal replacement therapy (RRT) is increasing dramatically every year (1). Among the modalities of RRT, peritoneal dialysis (PD) is a cost-effective modality that has been proven in numerous studies to ensure the patient's survival is equivalent to hemodialysis (2). Thus, health policymakers in many countries follow PD development policy (3). In Iran, there are currently 17.6 per million patients (pmp) with renal

stage PD, while in Qatar, they are 104.5 pmp on PD, since the growth of this modality in the Far East and the United States has been high in recent years (3-5).

Peritonitis is one of the most significant complications associated with PD and is one of the most significant causes of failure of this modality in time (6). During peritonitis, the peritoneal membrane undergoes structural and functional changes which are mediated by interleukin-1 beta (IL-1 β) (7,8). The NOD-like receptor protein (NLRP3) inflammasome, a caspase-1 activating

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multiprotein oligomer, links microbial assay and stress to the activation of proinflammatory cytokines, including IL-1 β , whose activation appears to play an important role in several pathological inflammatory conditions. The NLRP3 inflammasome is activated in acute peritonitis in patients undergoing PD, and this activation is associated with the release of IL-1 β in dialysis (8).

Uric acid (UA) is the final product of purine breakdown or nucleotide metabolism via xanthine oxidase or xanthine dehydrogenase and most of it is excreted by the kidney (6). In recent years, some studies have indicated an association between serum UA (sUA) levels in the blood and mortality in PD patients (9,10). Some studies have suggested that sUA is one of the factors influencing the process of systemic inflammation in patients with renal impairment (6,11,12). UA crystals have been shown to induce inflammation mediated by IL-1 β and activation of NLRP3 (13).

Taking into account the importance of peritonitis and its role in the failure of dialysis modality and mortality and morbidity of patients, finding clues with predictive value for peritonitis risk in these patients can help to reduce the failure and complications of this technique.

Objectives

This study sought to estimate the relationship between sUA levels and inflammatory markers and the incidence of peritonitis in PD patients, to form the basis of future therapeutic intervention studies aimed at reducing the risk of peritonitis in dialysis.

Patients and Methods

Study design

The purpose of this study was investigating the relationship between levels of UA and peritonitis as a retrospective cohort over the six years between March 2011 and August 2017 at the PD centers affiliated to Kerman university of medical sciences. Our statistical population consisted of all PD patients at Kerman PD centers over those six years. As a first step, the records of all patients who underwent PD at the Kerman centers were reviewed. Our inclusion criteria applied to all patients who underwent PD for six months or more, between March 2011 and August 2017. Exclusion criteria were: 1. Patients who underwent UA-reducing treatments such as allopurinol before and during dialysis. 2. Patients with incomplete clinical records.

Finally, 151 PD patients were evaluated after entering the preliminary information, demographic characteristics (age, gender, weight, body mass index [BMI], location and education level) and levels of UA, albumin, ferritin, calcium, phosphorus, hemoglobin and creatinine were collected at the beginning and until August 2017 based on the data recorded in their files. Then, patients were divided into two groups based on the serum levels of UA. Group one with UA above 6.5 mg/dL and group two with sUA less than and equal to 6.5 mg/dL. Inflammatory

factors including ferritin, albumin, hemoglobin and the incidence of peritonitis (as the amount of more than 100 white blood cells or more than 50% of neutrophils in the output fluid of PD or positive culture of peritoneal fluid) were compared between two groups. The outcome of peritonitis was considered.

Statistical analysis

After extracting and recording the data, the study data were analyzed by SPSS software version 25 (SPSS Inc., Chicago, IL). Mean \pm SD was conducted to report quantitative variables in the case of normal distribution, and medians (interquartile ranges) were used in abnormal distribution. Qualitative variables were reported as numbers and percentages. To compare the mean level of the inflammatory markers between two groups, independent *t* test, Mann-Whitney U and chi-square tests were employed. A $P < 0.05$ was considered statistically significant.

Results

In this study, 151 PD patients were studied, of which 68 (45%) were male and 83 (55%) females. The mean age of the patients was 53.99 ± 17.24 years with the mean weight of 60.32 ± 14 kg. The majorities of them living in urban areas (76.8%), employed (21.2%), and had a diploma or lower degree (55%). Hypertension was the most common cause of kidney failure in our study population [36 patients (23.8%)] and had the highest frequency among underlying comorbidities [44 patients (29.1%)].

Of total participants, around 100 patients (66.2%) had sUA level less than or equal to 6.5 mg/dL and 51 patients (33.7%) were with sUA level more than 6.5 mg/dL. In the group with sUA level more than 6.5 mg/dL, the number of males was more than females (52% versus 48%) and in the group with less sUA equal to 6.5 mg/dL, the number of women more than men (68.6% versus 31.4%). There was no statistically significant difference between the two groups in terms of age, weight and initial peritoneal equilibration test (PET); however, there was a significant difference between the two groups in terms of gender. The mean level of hemoglobin was significantly lower in patients with higher sUA level ($P = 0.002$). The mean level of albumin ($P = 0.002$), phosphorus ($P = 0.004$), and creatinine ($P = 0.02$) was significantly lower in patients with sUA below 6.5 mg/dL. Table 1 shows the comparison of patients' characteristics and biochemical variables between two groups.

Peritonitis was observed in 72 (47.6%) patients. The frequency of peritonitis in the group with higher level of UA (51%) was higher than the group with lower level (46%), but this difference was not statistically significant ($P = 0.56$).

Patients reclassified in the following four groups by sUA level; group one with sUA level ≤ 3.5 mg/dL; group two with a level of 3.5-6.5 mg/dL; group three with a level of

Table 1. Patients' characteristics and biochemical variables by UA levels

Variable	UA≤6.5 mg/dL (n = 100)	UA>6.5 mg/dL (n = 51)	P value
Age (y)	55.37 ± 16.47	51.34 ± 18.50	0.18 ^a
Gender, No. (%)			
Male	52 (52)	16 (31.4)	0.01 ^a
Female	48 (48)	35 (68.6)	
Weight (kg)	60.80 ± 14.13	59.35 ± 13.84	0.57 ^a
BMI (kg/m ²)	24.13 ± 5.55	22.11 ± 4.21	0.45 ^a
Ferritin (ng/mL)	466.88 ± 37.34	391.53 ± 39.73	0.32 ^b
Hemoglobin (g/dL)	10.90 ± 0.17	9.93 ± 0.26	0.002 ^c
ALB (g/dL)	3.76 ± 0.05	4.06 ± 0.07	0.002 ^c
Ca (mg/dL)	7.25 ± 0.22	8.25 ± 0.18	0.13 ^b
P (mg/dL)	5.10 ± 0.12	5.55 ± 0.14	0.004 ^b
Creatinine (mg/dL)	7.02 ± 0.26	8.14 ± 0.38	0.016 ^c
PTH (pg/mL)	188.82 ± 22.16	254.23 ± 41.28	0.13 ^c
Systolic blood pressure (mm Hg)	134.16 ± 1.86	132.25 ± 2.83	0.56 ^c
Diastolic Blood Pressure (mm Hg)	78.92 ± 1.19	77.79 ± 1.53	0.79 ^b
History of peritonitis, No. (%)			0.49 ^a
Yes	46 (46)	26 (51)	
No	54 (54)	25 (49)	
PET, No. (%)			0.82 ^a
Low	10 (10)	9 (17.6)	
Low average	19 (19)	12 (23.5)	
High average	41 (41)	18 (35.4)	
High	30 (30)	12 (23.5)	

Data presented as mean ± standard deviation; BMI: Body mass index, ALB: Albumin, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, PET; initial peritoneal equilibration test

^aBased on chi-squared test, ^bBased on Mann-Whitney U test, ^cBased on independent samples t test.

Table 2. Determination of peritonitis frequency based on UA level

Variable, No. (%)	UA≤3.5 mg/dL	3.5 <UA≤6.5	6.5 <UA≤8	UA≥8mg/dL	P value	
	3 (2)	97 (64.2)	37 (24.5)	N=14 (9.3)		
History of peritonitis, No. (%)	Yes	3 (100)	43 (44.3)	18 (48.6)	8 (57.1)	0.236
	No	0 (0)	54 (55.7)	19 (51.4)	6 (42.9)	

6.5–8 mg/dL; group four with a level of ≥8 mg/dL. Table 2 shows the determination of peritonitis frequency based on sUA level. Peritonitis was observed in group one in three (100%) patients; group two with 43 patients; group three with 18 patients and group four with 8 patients. This discrepancy was not statistically significant ($P = 0.236$).

In the group of patients with peritonitis, the number of women was more than men (63.5% versus 36.5%) and in the group of patients without peritonitis, the number of men was more than women (53.2% versus 46.8). Most patients of both groups lived in urban areas (with peritonitis (73%) and no peritonitis (82.7%) and had a diploma and lower education (with peritonitis (59.7%) and no peritonitis (59.7%). The mean age of patients in

the group with peritonitis (52.16 ± 17.19) years was lower than the group without peritonitis (55.79 ± 17.21) years, and the mean weight of patients with peritonitis (59.69 ± 13.8 kg) was less than the mean weight in the group with no peritonitis (60.95 ± 14.28 kg). Table 3 shows patient characteristics and biochemical variables based on the history of peritonitis. There was no significant difference between the two groups in terms of education, age, and weight; however, there was a significant difference between the two groups in terms of gender. The mean levels of albumin ($P=0.90$) and ferritin ($P=0.85$) were lower for patients without peritonitis than those with peritonitis, but these differences were not statistically relevant. Furthermore, the average hemoglobin level in

Table 3. Patients' characteristics and biochemical variables by history of peritonitis

Variable	History of peritonitis		P value
	Yes (n=72)	No (n=79)	
Age (y)	52.16±17.19	55.79±17.21	0.21
Gender, No. (%)			
Male	27 (36.5)	41 (53.2)	0.03
Female	47 (63.5)	36 (46.8)	
Weight (kg)	59.69±13.8	60.95±14.28	0.59
BMI (kg/m ²)	24.67±8.10	22.41±4.88	0.34
Ferritin (ng/mL)	443.36±41	436.29±38.9	0.90
Hemoglobin (g/dL)	10.30±0.19	10.76±0.22	0.12
ALB (g/dL)	3.87±0.06	3.85±0.06	0.85

patients without peritonitis was higher than in patients with peritonitis, nonetheless this difference was not statistically significant ($P=0.127$).

Discussion

This retrospective cohort study reviewed the relationship between sUA levels and the incidence of peritonitis in PD patients. Peritonitis is one of the leading causes of PD failure and a leading cause of morbidity and mortality in these patients (6). As a result, several studies over the years have investigated peritonitis-related risk factors such as age, gender, nutritional status, weight, and electrolytes in PD patients (14-18) and older (14), females (14), hypoalbuminemia (15), obesity (16) and hyponatremia (17) have been suggested as risk factors for peritonitis in this group of patients. Peritonitis was higher in females in our study, and the gender difference was statistically significant. There was no distinction between the age, weight, and albumin between the two groups with and without peritonitis.

The prevalence of peritonitis was 49%. Comparison of the frequency distribution of peritonitis in two groups with less and equal to sUA equal to 6.5 mg/dL and more than 6.5 mg/dL by chi-square test showed, the frequency of peritonitis in the group with high sUA (51%) was higher than the group with less UA equal to 6.5 mg/dL (46%). This difference was not statistically significant. Our study also found that the risk of peritonitis increases gradually as sUA levels rise (Table 3). However, we could not find a significant relationship between peritonitis and UA. It should remember that our sample size was relatively small, and we measured the average UA over time, not at the time of peritonitis.

In 2017, a study by Hsieh et al in Taiwan with 371 PD patients examining the causes of PD failure concluded that high sUA levels were associated with PD technique failure associated with all causes, including peritonitis (6). Although no study other than the study by Hsieh et al has demonstrated a relationship between UA levels and

peritonitis in PD patients, other studies have reported the role of UA in infections in both dialysis (19) and non-dialysis patients (20,21). In 2020, a study of 1486 hemodialysis patients were performed in Japan. Serum UA levels were measured before dialysis. Patients were categorized into five groups according to their sUA level at the start of dialysis: G1 serum with UA level <6 mg/dL. G2, with a level of 6.0-8.0 mg/dL; G3, with a level of 8.0-10.0 mg/dL; G4 with a level of 10.0-12.0 mg/dL; and G5, with a level of 12.0 mg/dL. The study concluded that severe hyperuricemia (sUA level ≥ 12.0 mg/dL) at the start of hemodialysis is a risk factor for death from infection (18).

According to a 2020 study conducted in Korea with 173 209 participants, 8809 of whom had sUA levels above 6 mg/dL in females and over 7 mg/dL in males, the study concluded that hyperuricemia was associated with periodontitis. The study suggests that increased sUA levels may have a positive effect on periodontitis and oral infections (19). A 2015 study of 144 patients with sepsis found that high UA levels were associated with poor prognosis in sepsis patients (20). Another Belgian study of 399 patients with various central nervous system (CNS) infections and its association with sUA levels found that, patients with CNS infections had lower sUA levels while the sUA value increased after treatment. Therefore, UA level changes may indicate clinical therapeutic effects in patients with CNS infection (21). Since one of the presumptions of the effect of UA on infections is to reduce. Its antioxidant effects and increase the production of reactive oxygen species (ROS) in both hyperuricemia and at reduced levels below 3.5 mg/dL and a significant increase in markers of fibrosis, inflammation, and oxidative stress in Mice with both low sUA and high blood UA levels have been observed (22). In our study, only three participants had sUA levels below 3.5 mg/dL, and all three had peritonitis. Not only due to the small number of this group, our study was not statistically significant in the group below 3.5 mg/dL, but it is also important to note that all of them had peritonitis.

In addition to the effects of UA on ROS production, hyperuricemia has also been shown to stimulate the production of interleukin-1 β , IL-6, and tumor necrosis factor, stimulating proinflammatory mechanisms and the effect of signals by interleukin-1 β , IL-6. And tumor necrosis factor on macrophages and dendrocytes reduces their response, including in the peritoneum (6, 11). Another finding in our study was that in patients with sUA more than 6.5 mg/dL, hemoglobin was significantly lower than in people with sUA below 6.5 mg/dL. Additionally, in people with sUA below 6.5 mg/dL albumin, phosphorus levels and creatinine were statistically significantly lower than those with sUA above 6.5 mg/dL were. In recent years, several studies have examined the relationship between sUA levels and mortality and nutritional status

in hemodialysis patients (23,24) and non-dialysis patients (24,25), and PD patients (9,10,26). In the studies by Tseng et al and Cang et al, it was found that both high sUA levels (above 8 mg/dL) and low sUA levels (less than 4 mg/dL) in the elderly — especially in malnourished people — was associated with mortality from all causes, especially cardiovascular disease (24,25). In the study by Tseng et al, low albumin malnutrition and low BMI were associated with levels below 4 mg/dL UA24(). A study of 728 PD patients found that sUA levels below 360 $\mu\text{mol/L}$ (equivalent to 6 mg/dL) indicated a higher risk of cardiovascular events. In these patients, low sUA levels were associated with lower serum albumin levels and suboptimal nutritional status, as well as lower BMI and phosphorus (26).

A study in Korea showed no association between anemia and hyperuricemia in people without chronic kidney disease. In patients with chronic kidney disease, anemia doubled the risk of hyperuricemia, and this association remained significant when adjusting glomerular filtration rate. In subgroup analyzes, the association between anemia and hyperuricemia was significant in people ≥ 65 years of age and in people with diabetes or hypertension (27).

Conclusion

Our study showed that the frequency of peritonitis in the group with sUA higher than 6.5 mg/dL, was higher and also hemoglobin was significantly lower, in the group with sUA less and equal to 6.5 mg/dL, albumin, phosphorus and creatinine levels was lower. Therefore, it seems that serum sUA can be studied more widely in PD patients as an indicator in predicting infection, anemia and nutritional status.

Limitations of the study

Our study, along with strengths such as addressing the cheap and available UA index for predicting the critical complication of peritonitis, which, as mentioned, was addressed in only one study, has odorous limitations. The most important limitation of our study was its retrospective nature and the use of patients' records. Therefore, due to this retrospective nature, UA and other laboratory indicators were measured in different laboratories and at different times. Although we excluded subjects treated with allopurinol, most of the subjects were treated with different doses of furosemide at different times; we could not eliminate the confounding effect of this drug on patients.

Therefore, due to these limitations, an indigenous study to evaluate the cheap and available UA index in predicting infection in PD and hemodialysis patients, as well as studies with higher sample sizes to investigate the effect of UA on nutritional index and the effect of UA on anemia, dosage of erythropoietin is recommended in patients with chronic kidney disease and dialysis.

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Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kerman University of Medical Sciences under the ethical code #IR.KMU.AH.REC.1398.044. Written informed consent was obtained from all participants prior to any intervention. The data presented in this article were extracted from Zeinab Jafarian's residency thesis at Kerman University of Medical Sciences (Thesis #97000182). Furthermore, the authors have fully complied with ethical considerations, such as avoiding plagiarism, data fabrication, and double publication.

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