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Serum Uric Acid Level and Cardiovascular Risks in Hemodialysis Patients: An Algerian Cohort Study

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Abstract: Elevated Serum Uric Acid (SUA) was usually associated with an increased risk of cardiovascular events and mortality in general population. However, there are few reports concerning the clinical impact and the pathogenic role of Uric Acid (UA) in Hemodialysis (HD) patients. The aim of the study was to investigate the relationship between SUA and various Cardiovascular (CV) risk factors in HD patients. This retrospective; observational cohort study includes 45 HD patients with a mean age of 51.26±15.21 years. The differences of the CV risk factors between the patients according to their SUA levels were investigated. Age, Cardiovascular Diseases (CVD), increased creatinine, Fasting Blood Glucose (FBG), Corrected Calcium (cCa), Phosphate (P), cCa x P product and LDL cholesterol levels were associated with lower SUA levels, whereas higher SUA level was associated with Diabetes Mellitus (DM), hypertension and increased triglycerides level ($p<0.01$). In multiple regression analysis, history of diabetes ($\beta = 0.360$, $p<0.05$), reduced corrected serum calcium (cCa) ($\beta = -1.456$, $p<0.01$) and Phosphate (P) levels ($\beta = -1.752$, $p<0.01$) were predictive of an increased SUA concentration. Despite from what has been demonstrated in the general population and DM patients, a lower SUA level in HD patients was associated with higher cardiovascular risk factors and high co-morbidity burden. Moreover, higher SUA concentrations may be cardioprotective in dialysis patients.

Key words: Hemodialysis, uric acid, cardiovascular risks

INTRODUCTION

Cardiovascular Disease (CVD) is the primary cause of death of End-Stage Renal Disease (ESRD) patients and intensive management of Cardiovascular (CV) risk factors, including age, hypertension, dyslipidemia, smoking, etc., has been proposed in order to reduce the burden of CVD in Hemodialysis (HD) patients (Sarnak *et al*., 2003; Masoudi *et al*., 2004; Lindner *et al*., 1974; Foley *et al*., 1998).

To help assess cardiovascular risk in HD patients, numerous new markers of cardiovascular risk like high hs-CRP, Homocysteine (Hcy) and Lp(a) levels, inflammation, oxidative stress, have been introduced and utilized in outcome studies (Cases *et al*., 2002; Bayres *et al*., 2003; Ohkuma *et al*., 2003; Yilmaz *et al*., 2005).

Uric Acid (UA) is the final oxidation product of purine catabolism, produced by metabolism of dietary and endogenous nucleic acids. Because most UA is excreted from the kidney, hyperuricemia is usually seen in renal insufficiency patients and maintenance HD patients.

Several large epidemiologic studies have reported that elevated Serum Uric Acid (SUA) concentration is associated with CVD (Hoieggen *et al*., 2004; Fang and Alderman, 2000; Niskanen *et al*., 2004). Some investigators have suggested that UA plays a causal role in the development of CVD (Johnson *et al*., 1999), whereas others have concluded that UA merely reflects other concomitant risk factors, such as hypertension, insulin resistance, or dyslipidemia (Culleton *et al*., 1999). An elevated SUA level was also associated with the progression of kidney disease in the normal population and in patients with hypertension, diabetes and chronic kidney disease (CKD) (Iseki *et al*., 2001; Segura *et al*., 2002; Syrjanen *et al*., 2000; Tseng, 2005).

Despite, several large cohort studies several large have demonstrated associations between SUA levels and cardiovascular disease in the general population and in

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patients with hypertension and cardiovascular disease, there are few report concerning the clinical impact and the pathogenic role of UA in HD patients.

This study was therefore designed to explore the prevalence of hyperuricaemia in continuous HD patients and to investigate the possible associations between SUA and CV risk factors in a cohort of Algerian HD patients.

MATERIALS AND METHODS

Study design and subjects: This is a retrospective cohort study which included 45 consecutive chronic renal patients receiving maintenance hemodialysis on the hemodialysis unit of IBN ZOHR hospital of Guelma (East of Algeria), followed up between June 2011 and January 2013.

All patients underwent routine hemodialysis three times a week for at least 4 h, using bicarbonate-containing dialyzed fluid.

Baseline demographic and medical data was also abstracted from dialysis records including age, sex and blood pressure, primary renal disease, duration of dialysis and presence of co-morbid factors (diabetes and cardiovascular disease) (Table 1).

Measurements: Blood samples were collected after 10 h fasting. They were evaluated for Fasting Blood Glucose (FBG), UA, cholesterol, triglyceride, High-density Lipoprotein Cholesterol (HDLC), Low Density Lipoprotein Cholesterol (LDLC), albumin (bromocresol green method), hematocrit, urea (urease/peroxidase method), creatinine (kinetic Jaffe method), corrected serum calciu (cCa), Phosphate (P), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP) and ferritin levels.

FBG was measured by the glucose oxidase method. Total cholesterol, triglyceride and HDL levels were measured by an enzymatic method (Spinreact, Spain). The LDLC was calculated according to Friedwall formula in patients with a triglyceride level less than 4.5 mmol L^{-1}. Serum calcium was corrected (cCa) for serum albumin according to the formula:

$$cCa\ (mg\ L^{-1}) = calcium\ (mg\ L^{-1}) + 0.8 \times (40 - albumin\ (g\ L^{-1}))$$

SUA concentrations were measured by enzymatic colorimetric method (uricase/peroxidase). Patients were stratified into the following groups according to the concentration of SUA: Group I≤192 μmol L^{-1} (20th percentile); group II, 192-429 μmol L^{-1} (20-80th percentile); group III≥430 μmol L^{-1} (>80th percentile).

Table 1: Demographic and clinical baseline characteristics of HD patients

Characteristic	Values
Demographics	
Gender (male/female)	20/25
Age (years)	51.26±15.21*
DHD (months)	1603±1207
Etiology of ESRD	
Chronic glomerulonephritis	11.1
Polycystic kidney disease	4.4
Diabetic nephropathy	11.1
Obstructive uropathy	2.2
Hypertensive nephropathy	4.4
Others	6.6
Undetermined	53.3
Co-morbid factors	
DM (%)	31.11
Hypertension (%)	35.5
CVD (%)	44.4
Dyslipidemia (%)	26.66
Laboratory data	
UA (μmol L^{-1})	295.89±122.21
Creatinine (μmol L^{-1})	673.92±226.92
Urea (mmol L^{-1})	26.19±9.69
FBS (mmol L^{-1})	6.57±3.69
Albumin (g L^{-1})	37.95±9.51
Hematocrit (%)	27.86±7.46
AST (UI L^{-1})	21.26±15.36
ALT (UI L^{-1})	16.53±12.37
ALP (UI L^{-1})	267.68±137.96
cCa (mmol L^{-1})	2.38±0.55
P (mmol L^{-1}	1.61±0.48
cCa × P ($mmol^2/L^2$)	3,89±1.73
Ferritin (ng mL^{-1})	539.48±325.21
TC (mmol L^{-1})	4.82±1.14
TG (mmol L^{-1})	1.72±0.91
LDL-C (mmol L^{-1})	3.31±1.06
HDL-C (mmol L^{-1})	0.80±0.32
Atherogenic index (TC/HDL-C)	6.68±3.21

*Mean±SD (n = 45) DHD: Duration of hemodialysis treatment, DM: Diabetes mellitus, CVD: Cardiovascular disease: AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, cCa: Calcium corrected by serum albumin, P: Phosphate, TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol

All biochemical analyses were performed with ERBA XL 200 Automatic Analyzer (GmbH, Germany) under good quality control (coefficient of variation routinely less than 3%). Ferritin was measured by Enzyme Linked Fluorescent Assay (ELFA) method (Mini-Vidas, BioMérieux, France).

Definition of CV risk factors: Cardiovascular disease was defined as the presence of previous myocardial infarction or cerebrovascular accidents based on the clinical history or physical examination. Hypertension was defined as a positive history of hypertension or use of antihypertensive agents at the time of HD commencement. We classified the subjects with diabetes as either alleged diabetes subjects or subjects with fasting glucose≥7.0 mmol L^{-1}.

Dyslipidemia was determined by a prior diagnosis of dyslipidemia, fasting serum low-density lipoprotein cholesterol (LDL-C)≥4.1 mmol L^{-1} or total cholesterol≥6.3 mmol L^{-1}.

Statistical analysis: Statistical analysis was performed using SPSS for Windows software, version 16.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as Mean±SD or percentage and a p-value<0.05 was considered statistically significant.

Student's t-test and one-way ANOVA were used to test for differences in categorical or continuous factors, respectively, between the different SUA level groups.

The relationship of uric acid with other adjusted variables was determined with Pearson's correlation analysis. To examine the effects of various factors on SUA concentration, the following factors were considered as independent variables for multiple regression analysis: age, male gender, duration of hemodialysis, history of diabetes, hypertension, CVD, creatinine, urea, FBG, hematocrit, albumin, ferritin, cCa, P, cCaxP, AST, ALT, ALP, total cholesterol, triglyceride, HDL-C, LDL-C and atherogenic index.

RESULTS

Of the forty five patients included in this study, 10 were men and 25 were women. The subjects ranged in age from 24 to 83 years (51.26±15.21 years). The mean duration of dialysis was 1603±1207 months (range, 325 to 5201 months). 31.11% (n = 14) of the patients had a diabetes, 35.5% (n = 16) were hypertensive and 44.4% (n = 20), had a cardiovascular disease and 26.6% (n = 12) had a dyslipidemia.

The most frequent etiology of underlying renal diseases was chronic glomerulonephritis (11.1%) and diabetic nephropathy (11.1%).

The mean SUA concentration at baseline was 295.89±122.21 μmol L^{-1} (range, 144 to 582 μmol L^{-1}) and the prevalence of hyperuricemia (UA> 420 μmol L^{-1}) was 26.6% for the whole group. The mean SUA level was higher in the men cohort (318.60±1.3) than in the women cohort (282.24±1.0). All demographic and medical data are shown in Table 1.

The comparison of baseline characteristics between the three SUA severity groups is shown in Table 2. Age, CVD, increased creatinine, FBG, corrected calcium, phosphate, cCa x P product and LDL cholesterol levels were associated with lower SUA levels, whereas higher SUA level was associated with diabetes mellitus, hypertension and increased triglycerides level (p<0.01).

In addition, there were no significant differences in male sex, duration of hemodialysis, dyslipidemia, levels of urea, hematocrit, albumin, ferritin, AST, ALT, ALP, total cholesterol, HDL-C and atherogenic index between the three groups.

Relationships between serum uric acid concentrations and other variables are shown in Table 3. Positive correlation was found between SUA and ALT level (r = 0.322, p = 0.031), whereas inverse correlation was found between SUA concentration and creatinine (r = -0.260, p = 0.035), phosphate (r = -0.289,

Table 2: Demographics, clinical and biochemical characteristics according to SUA levels

Characteristic	Group I SUA = 192 (μmol L^{-1}) (n = 10)	Group II SUA 192-429 μmol L^{-1} (n = 26)	Group III = 430 μmol L^{-1} (n = 9)	p-value
Male gender (%)	50	30.76	55.55	0.428
Age (years)	57.90±13.00*	51.00±16.32	44.67±12.43	<0.010
DHD (months)	1647.40±858.57	1684.38±1490.33	1321±365.42	0.150
DM (%)	10	21.21	55.55	<0.010
Hypertension (%)	20	30.30	50.0	<0.010
CVD (%)	70	30.30	33.33	<0.050
Dyslipidemia (%)	40	21.21	22.22	0.058
Creatinine (μmol L^{-1})	754.19±171.25	649.67±254.04	599.74±131.70	<0.010
Urea (mmol L^{-1})	25.30±9.15	26.97±10.48	26.64±7.99	0.554
FBG (mmol L^{-1})	8.35±5.10	6.71±3.49	5.49±1.94	<0.050
Albumin (g L^{-1})	36.20±5.1	39.0±10.09	36.78±11.37	0.798
Hematocrit (%)	29.22±8.98	28.08±7.41	25.75±6.00	0.268
AST (UI L^{-1})	20.50±6.8	18.46±11.11	30.22±17.28	0.075
ALT (UI L^{-1})	14.40±5.03	14.38±7.9	25.11±22.65	0.433
ALP (UI L^{-1})	249.0±138.52	261.38±120.37	306.67±188.53	0.713
cCa (mmol L^{-1})	2.46±0.31	2.42±0.67	2.15±0.33	<0.050
P (mmol L^{-1}	1.85±0.60	1.61±0.45	1.29±0.22	<0.010
cCa × P ($mmol^2/L^2$)	4.66±1.94	3.97±1.76	2.78±0.65	<0.010
Ferritin (ng mL^{-1})	542.50±313.77	554.32±351.53	493.26±286.34	0.730
TC (mmol L^{-1})	5.00±1.57	4.88±0.95	4.28±1.00	0.100
TG (mmol L^{-1})	1.74±0.51	1.58±0.66	2.16±1.64	<0.010
LDL-C (mmol L^{-1})	4.56±1.54	3.37±0.92	2.94±0.74	<0.050
HDL-C (mmol L^{-1})	0.82±0.28	0.74±0.23	0.82±0.54	0.053
Atherogenic index (TC/HDL-C)	6.31±1.78	6.90±3.76	6.47±2.9	0.984

*Data are expressed as Mean±SD

Table 3: Correlation of SUA levels and other parameters in whole HD patients

	SUA	
Characteristic	R	p-value
Age (years)	-0.204	0.179
DHD (months)	0.028	0.856
Creatinine (μmol L^{-1})	-0.260	<0.050
Urea (mmol L^{-1})	0.102	0.503
FBS (mmol L^{-1})	-0.155	0.301
Albumin (g L^{-1})	0.041	0.790
Hematocrit (%)	-0.213	0.166
AST (UI L^{-1})	0.293	0.054
ALT (UI L^{-1})	0.322	<0.050
ALP (UI L^{-1})	0.109	0.478
cCa (mmol L^{-1})	-0.266	0.078
P (mmol L^{-1}	-0.289	<0.050
cCa x P ($mmol^2/L^2$)	-0.328	<0.050
Ferritin (ng mL^{-1})	-0.092	0.546
TC (mmol L^{-1})	-0.317	<0.050
TG (mmol L^{-1})	0.090	0.556
LDL-C (mmol L^{-1})	-0.265	<0.050
HDL-C (mmol L^{-1})	-0.063	0.681
Atherogenic index (TC/HDL-C)	-0.068	0.659

Table 4: Multivariable Linear Regression for prediction of increased Serum Uric Acid (SUA) in HD patients

Variable	Standardized coefficient (β)	p-value
Age	-0.206	0.297
Gender (male)	0.126	0.120
DHD (%)	0.019	0.908
DM (%)	0.360	<0.050
Hypertension (%)	-0.040	0.782
CVD (%)	0.025	0.617
Dyslipdemia (%)	-0.235	0.586
Creatinine (μmol L^{-1})	-0.264	0.368
Urea (mmol L^{-1})	0.247	0.283
FBS (mmol L^{-1})	-0.279	0.135
Albumin (g L^{-1})	-0.009	0.976
Hematocrit (%)	-0.287	0.219
AST (UI L^{-1})	-0.031	0.927
ALT (UI L^{-1})	0.164	0.604
ALP (UI L^{-1})	0.088	0.626
cCa (mmol L^{-1})	-1.456	<0.010
P (mmol L^{-1}	-1.752	<0.010
cCa x P ($mmol^2/L^2$)	2.426	0.104
Ferritin (ng mL^{-1})	0.041	0.839
TC (mmol L^{-1})	-0.233	0.734
TG (mmol L^{-1})	0.142	0.620
LDL-C (mmol L^{-1})	0.039	0.957
HDL-C (mmol L^{-1})	-0.143	0.735
Atherogenic index (TC/HDL-C)	-0.233	0.638

p = 0.047), cCa×P (r = -0.328, p = 0.028), total cholesterol (r = -0.317, p = 0.034) and LDL-C levels (r = -0.265, p = 0.029). No significant correlations were found between SUA level and the rest of parameters.

On multivariable linear regression (R^2 = 0.431; p = 0.001; Table 4) history of diabetes (β = 0.360, p< 0.05), reduced corrected serum calcium (cCa) (β = -1.456, p<0.01) and Phosphate (P) levels (β = -1.752, p<0.01) were predictive of an increased SUA concentration.

DISCUSSION

Several studies have demonstrated that higher levels of SUA are associated with an increased risk of CVD and mortality in general population (9-11). However, in HD population, there is limited information on the relationship between SUA levels and CV factors.

In this cohort study, we investigated the relationship between SUA level and some CVD risk factors in HD patients. We found that hyperuricemia is common among ESRD patients in maintenance hemodialysis, occurring in 26.6% of the population, which was in agreement with findings of the previous reports (Suliman *et al*., 2006; Lee *et al*., 2009; Hsu *et al*., 2004; Latif *et al*., 2011).

Additionally, diabetics and hypertensive patients had higher SUA levels, suggesting a close relationship between SUA and these diseases (Table 2). Linear regression analysis demonstrated also, that diabetes mellitus was predictive of increased levels of SUA (β = 0.360, p<0.05) (Table 4).

Despite prospective clinical cohorts as well as several experimental studies that suggest UA could predict the development of vascular-related diseases like hypertension and diabetes (Feig *et al*., 2008), the pathogenic role of UA in the development and progression of hypertension and diabetes is still unclear. Indeed, elevated SUA levels in the general population are commonly seen in association with individual cardiovascular risk factors such as older age, hypercholesterolemia, hypertriglyceridemia, hypertension, hyperglycemia and obesity (Eckel *et al*., 2005). However, in the present study, HD patients with low SUA level were older and had significantly high prevalence of CVD (70%, p<0.05), increased FBG (8.35±5.10 mmol L^{-1}, p<0.05) and LDL cholesterol levels (4.56±1.54 mmol L^{-1}, p<0.05) compared with patients of normal and higher SUA level groups (Table 2). Furthermore, negative correlation was found between SUA concentration and levels of total cholesterol (r = -0.317, p = 0.034); LDL-C (r = -0.265, p<0.05); creatinine (r = -0.260, p<0.05); phosphate (r = -0.289, p<0.05) and cCa×P (r = -328, p<0.05) (Table 3).

These findings suggest that, distinct from what has been demonstrated in the general population and DM patients, a lower SUA level in HD patients was associated with higher cardiovascular risk factors and high co-morbidity burden. Moreover, higher SUA concentrations may be cardioprotective in dialysis patients.

Our data are in agreement with recent reports that underline the strong association between lower SUA level and higher risk of both death from all causes and cardiovascular disease in HD patients (Suliman *et al*.,

2006; Lee *et al*., 2009; Hsu *et al*., 2004; Latif *et al*., 2011). This paradox relationship, sometimes referred to as "reverse epidemiology" proved to be relatively constant in chronic hemodialysis. Reverse epidemiology is also found in HD patients for other CV risk factors, such obesity, hypertension, serum cholesterol or serum creatinine (Kalantar-Zadeh *et al*., 2003, 2005a, b; Kopple *et al*., 1999; Kunz and Hannedouche, 2009).

The potential mechanisms of the association between lower SUA level and increased risk of cardiovascular events in dialysis patients have yet to be elucidated.

It is well established that in HD patients increased Oxidative Stress (OS) and inflammation associated with atherosclerotic coronary artery disease and increased cardiovascular morbidity and mortality in HD patients (Oberg *et al*., 2004; Zoccali *et al*., 2004).

Uric acid has been shown to have antioxidant properties *in vitro* (Hink *et al*., 2002) and *in vivo* (Kandar *et al*., 2006), it contributes as much as 2/3rd of all free radical scavenging capacity in plasma (Squadrito *et al*., 2000) and it is particularly effective in quenching hydroxyl, superoxide, peroxal and peroxynitrite radical and may serve protective physiological role by preventing lipid per oxidation.

Urates possess preventive antioxidant property in addition to chain breaking antioxidant activity (Waring *et al*., 2001), this property may account for some of the benefit observed in the hemodialysis population.

In addition, uric acid was positively correlated with inflammatory markers and associated with nutrition status in HD patients (Caravaca *et al*., 2005; Lee *et al*., 2012; Lobo *et al*., 2012) and a low serum level of uric acid may have been a surrogate of poor protein intake and malnutrition in maintenance hemodialysis (Hsu *et al*., 2004).

This syndrome of malnutrition and protein energy wasting is often linked with increased oxidative stress and inflammation and it has been linked with increased mortality in HD patients.

In summary, HD patients have an increased cardiovascular risk that cannot be explained completely by traditional cardiovascular risk factors, this study showed that a lower SUA level was correlated with cardiovascular risk factors; older age, CVD, total cholesterol, LDL cholesterol and fasting blood glucose. In addition, a high SUA level was associated with diabetes mellitus and hypertension. This unexpected association may, in part, be explained by the antioxidant properties of uric acid in HD patients and its protective physiological role by preventing oxidative stress and lipid peroxydation. However, prospective long-term follow-up studies are needed to clarify the potential role of uric acid on overall and cardiovascular morbidity and mortality in HD patients.

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