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Impact of Hyperuricemia on Cardiovascular System in ESRD Patients

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Abstract

Background: Hyperuricemia was found to be associated with hypertension, coronary heart disease, metabolic syndrome and chronic kidney disease. However there are no specific data about the relationship of uric acid to cardiovascular disease and mortality in ESRD patients on chronic hemodialysis. **So, we aimed to** study the impact of hyperuricemia on cardiovascular system in chronic kidney disease and in ESRD patients on regular hemodialysis

Patients and methods: This study included 100 patients in Ashmoun hospital, nephrology department. Patients were chosen and divided into two groups: ***Group A,* 50**cases with chronic kidney disease and ***Group B,* 50**cases of ESRD on regular hemodialysis. All cases were subjected to full clinical examination, measurement of eGFR, laboratory tests for blood urea, serum creatinine and serum uric acid and ECG.

Results: Serum uric acid was significantly higher in dialysis group than CKD group ***(p<0.01).*** There was a highly significant correlation between uric acid and both systolic and diastolic blood pressure in Group A ***(all p values <0.01).*** Also, there was a significant correlation between serum uric acid and eGFR ***(p<0.05).***No significant difference found between Group A and group B as regards ECG findings ***(p>0.05).***

Conclusion: **In cases of CKD** uric acid is involved in the pathogenesis of renal failure and hypertension. **In patients with ESRD**, hyperuricemia is not a risk factor for the development of cardiac disease; but it shows reversed epidemiology and becomes a marker of good nutritious status. Further studies should be done on wider scales to evaluate the impact of hyperuricemia on cardiovascular system in hemodialysis patients.

Key words: Hyperuricemia- chronic kidney disease- ESRD- Cardiovascular risk

INTRODUCTION

Previous studies have shown that gout is associated with increased risk for cardiovascular mortality in the general population ***(1,2,3,4).*** Also, hyperuricemia is found to be associated with hypertension, coronary heart disease ***(5)***, metabolic syndrome ***(6)*** and chronic kidney disease ***(7).*** Cardiovascular disease is the leading cause of morbidity and mortality in chronic kidney disease (CKD) and in end stage renal disease (ESRD) ***(8).***

In patients of ESRD on hemodialysis, some studies described hyperuricemia as a factor which increases mortality ***(1,9,10).*** Other studies described the opposite completely and concluded that low level of uric acid is a risk factor of mortality among patients on hemodialysis ***(8,11).***

So, we aimed to study the impact of hyperuricemia on cardiovascular system in chronic kidney disease and in ESRD patients on regular hemodialysis.

Patients and methods

This observational study was conducted in Ashmoun hospital; nephrology department.100 patients were chosen and divided into two groups. **Group A,** composed of50 Cases with chronic kidney disease and **Group B,** composed of50 Cases of ESRD (End Stage Renal Disease) on regular hemodialysis.

All the participating patients were subjected to full history taking and clinical examination including measurement of body mass index (BMI).Estimated glomerular filtration rate (eGFR) was done using the MDRD equation recommended by the national kidney foundation.

$$GFR=170 \times SCr^{-0.999} \times SUN^{-0.170} \times SAlb+0.318 \times age^{-0.176}$$

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× 1.180 if black or 0.762 if female.
(ml/minute/1.73m²) =100-130ml/minute/1.73m².
Patients were also subjected to laboratory investigations including measurement of serum urea, creatinine, uric acid and hemoglobin %.
Electrocardiogram (ECG) was also performed for all cases.

Exclusion criteria:

Patients with advanced heart failure, advanced liver cell failure, malignant or blood diseases were excluded. Patients on treatment that affects serum uric acid level as diuretics and allopurinol were also excluded.

Statistical Analysis:

Analysis of data was done by an IBM computer using SPSS (statistical program for social science version 16). Quantitative data were expressed as **mean and SD** while qualitative data were expressed as **number and percentage. Unpaired t-test** was used to compare two groups as regards their quantitative data while **chi-square test** was used to compare two groups as regards their qualitative data. **Pearson correlation coefficient** test was used to correlate between two different variables with quantitative data.
P value >0.05 was considered insignificant while P<0.05 was considered significant. P value<0.01 and <0.001 were considered highly significant.

RESULTS

In our observational study, 100 patients were chosen. Patients were divided into 2groups: ***Group A*** which included 50 cases with chronic kidney disease and ***Group B*** which included 50 cases of ESRD on regular hemodialysis. Both groups were found to be matched as regards age and BMI making them liable for comparison.

Discussion:

In our observational study, we included 100 patients and divided them into two groups, ***Group A :*** 50 Case with chronic kidney disease and ***Group B:***50 Cases with ESRD on regular hemodialysis.

We found that, serum uric acid was significantly higher in ESRD patients than in CKD patients ***(p<0.01).*** Also, there was a negative significant correlation between serum uric acid and eGFR ***(p<0.05).*** Both results support that uric acid is linked to deterioration of renal function. Our results agreed with studies which reported that high serum uric acid level is associated with decline in renal function and GFR***(7,12).*** Mechanism by which uric acid cause damage to the kidney includes glomerular hypertension and cortical vasoconstriction, which may induce glomerular damage and tubular ischemia, in addition to uric acid stimulated inflammatory response ***(13).***

In CKD patients, we found a highly significant correlation between serum uric acid level and both systolic and diastolic blood pressures ***(p values<0.01)*** which reflects the correlation of hyperuricemia to hypertension. There was also a negative significant correlation between eGFR and systolic blood pressure ***(p<0.05)*** accompanied by a highly significant negative correlation between eGFR and diastolic blood pressure ***(p<0.01)*** .Our results agrees with ***Mazzali et al*** who added that the increase in serum uric acid in hypertensive patients is due to decrease in the renal blood flow that accompanies the hypertensive state***(14).***The mechanism of hypertension was shown to be caused by a uric acid mediated reduction in **endothelial** nitric oxide levels and stimulation of renin expression***(15).*** Moreover, several studies reported that lowering uric acid with xanthine oxidase inhibitors improves endothelial function ***(12).***

In hemodialysis patients, serum uric acid was significantly higher in ESRD patients than in CKD patients ***(p<0.01)***.A number of factors regulate serum uric acid in hemodialysis patients. Dietary intake of purines and fructose is a primary source of uric acid. Since the kidney eliminates much of the uric acid generated, a decrease in the GFR is associated with increase in serum uric acid level (in spite of the compensatory increase in gut elimination and in spite of increased degradation pathway by 5 folds) ***(16).*** Being an antioxidant, the degradation of uric is also through its reaction with oxidants to produce allantoin and other products ***(17).***

The significant increase in serum uric acid in hemodialysis patients was not reflected on ECG findings. There was no significant difference between both group as regards ECG

findings ***(p>0.05)*** denoting that hyperuricemia is not a risk factor for the development of **cardiac disease**. Our results came in contrast with the study of ***Scott et al*** who reported that gout is associated with 1.5 fold increase in mortality risk in patients with ESRD without an obvious mechanism***(1).***Meanwhile, ***Walead et al*** reported that high uric acid lowers death risk in hemodialysis patients. He performed a study of 5,827 hemodialysis patients from six countries and concluded that those with uric acid levels below 8.2 mg/dl had a 24% and 54% increased risk of all-cause and cardiovascular mortality, respectively, compared with patients who had higher uric acid levels and that Each 1 mg/dl increment in uric acid was associated with a 5% decreased risk of all-cause mortality and 8% decreased risk of cardiovascular mortality ***(8).*** They attributed this protective effect of uric acid to its antioxidant property***(8).Kurt lee***, also, reported that low serum uric acid level is a risk factor for death in hemodialysis patients ***(11).*** The profound relationship between low serum uric acid and mortality is protein energy wasting ***(18).***Some authors suggested that high serum uric acid in CKD is a comorbid condition which shows the phenomenon of reversed epidemiology pattern in HD patients i.e. it becomes a beneficial agent through its antioxidant effect and being a marker of good nutritious state ***(8,11,19,20).***

In our study, we found that, serum uric acid and creatinine were significantly higher in ESRD patients than in CKD patients ***(p values<0.01).***Moreover, there was no significant difference between groups A and B as regards BMI. This leads us to report as Walead *et al*. and speculate that higher uric acid among hemodialysis patients is a surrogate for better nutritious status ***(8).***

So, **we conclude** that, in **cases of CKD** uric acid is involved in the pathogenesis of renal failure and hypertension .**In ESRD** patients it is not a risk factor for the development of cardiac disease; but it shows reversed epidemiology and becomes a marker of good nutritious status. Further studies should be done on wider scales to evaluate the impact of hyperuricemia on cardiovascular system in hemodialysis patients.

References;

1. ***ScottD Cohen, Paul Kimmel, Lawrence Agodoa, et al (2008)***: association of incident gout and mortality in dialysis patients.***J Am Soc Nephrol. 19(11):2204-2210.***
2. ***Francesca Viazzi,Denise Parodi, Giovanna Leoncini, et al (2005)***:serum uric acid and target organ damage in primary hypertension**.** ***Hypertension.45:991.***
3. **Waring WS, Webb DJ, Maxwell SRJ, et al (2000)**: Effect of local hyperuricemia on endothelial function in human forearm vascular bed.***Br J Clin Pharmacol. 49:511.***
4. ***Doehner W, Schoene N, rauchhaus M, et al (2002)***: Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure; results from 2placebo-controlled studies. ***Circulation, 105:2619-2624.***
5. ***Alper AB, Chen W, Yau L, et al (2005)***: childhood uric acid predicts adult blood pressure: the Bogalusa heart study. ***Hypertension. 45:34-38.***
6. ***Nakagawa T, Mazzali M, Kang DH, et al (2003)***: Hyperuricemia causes glomerular hypertrophy in rats. ***AM J Nephrol. 23:2-7.***
7. ***Chien KL, Ching HC, Sung Fc, et al (2005):*** Hyperuricemia as a risk factor on cardiovascular events in Taiwan: The chin-shan community cardiovascular cohort study. ***Atherosclerosis. 183:147-155.***
8. ***Walead Latif, Angelo Karaboyas, Lin Tong, et al (2011):*** Uric acid levels and all-cause and cardiovascular mortality in hemodialysis population. ***Clin J Am Soc Nephrol. Online publication on 25th August 2011.6:1-8.***
9. ***Suliman ME, Johnson RJ, Garcia-Lopez E, et al (2006):*** J shaped mortality relationship for uric acid in CKD. ***Am J Kidney Dis. 48:761-771.***
10. ***Hsu SP,Pai MF, Peng YS, et al (2004)***: Serum uric acid levels show a J shaped association with all-cause mortality in hemodialysis patients. ***Nephrol Dial Transplant. 19:457-462.***

11. ***S M Kurt lee, Andrew L Lee, Thomas J winters, et al (2009):*** Low serum uric acid levelis a risk factor for death in incident hemodialysis patients. ***Am J Nephrol. 29(2):79-85.***
12. ***Johnson RJ, Kang DH, Feig DI, et al (2003):*** Is there a pathologic role for uric acid in hypertension, and cardiovascular and renal disease?.***Hypertension. 41:1183-1190.***
13. ***Sanchez-lozada LG, Tapia E, Avila-Casado C, et al (2002):*** Mil hyperuricemia induces glomerular hypertension in normal rats. Renal physiology in ***Am J Physiol. 283:1105-1110.***
14. ***Mazzali M, Hughes J, Kim YG, et al (2001):*** Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. ***Hypertension. 38:1101-1106.***
15. ***Johnson RJ, Feig DI, Herrera-Acosta J, et al (2005):*** Resurrection of uric acid as a causal risk factor in essential hypertension. ***Hypertension. 45:18-20.***
16. ***Sorenson LB (1965)***: Role of the intestinal tract in the elimination of uric acid. ***Arthritis Rheum. 8:694-706.***
17. ***Kandar R, Zakova P, Muzakaova V (2006)***: Monitoring of antioxidant properties of uric acid in human for a consideration measuring of level of allantoin in plasma by liquid chromatography. ***Clin Chim Acta. 365:249-256.***
18. ***Goodkin DA, Young EW, Kurokawa K, et al (2004):*** Mortality among hemodialysis patients in Europe, Japan and United States: case mix effects. ***Am J Kidney Dis. 44(2): 16-21.***
19. ***Kopple JG (2005):*** The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. ***Am J Clin Nutr. 81:1257-1266.***
20. ***Kalanter-Zadeh K, Block G, Humphreys MH, et al (2003):*** Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. ***Kidney Int. 63:793-808.***

Table (1**): Shows comparison between group A and group B as regards clinical and laboratory parameters.**

	Group A (N=50)	Group B (N=50)	t-value	p-value
Age	**53.80±9.57**	**51.26±10.17**	**1.29**	**0.201**
BMI	**26.4 ± 3.64**	**25.55±6.17**	**0.84**	**0.404**
Diastolic B.P	**82.67±13.21**	**85.20 ± 13.73**	**0.94**	**0.350**
Systolic B P	**134.67±23.6**	**136.80±24.61**	**0.44**	**0.660**
Hemoglobin	**9.07 ± 1.01**	**8.86 ± 2.15**	**0.63**	**0.533**
S. Uric Acid	**6.51 ± 1.51**	**8.01 ± 1.95**	**4.30**	**0.001**
S. creatinine	**3.48 ± 1.02**	**9.45 ± 2.6**	**15.11**	**0.001**
Blood urea	**86.29 ± 33.1**	**134.34±35.43**	**7.01**	**0.001**

From table1, we can see that there is highly significant difference between Group A and Group B as regards serum uric acid , serum creatinine and blood urea***(all p values <0.01).*** Meanwhile, there was insignificant difference as regards blood pressure and hemoglobin **(all p values>0.05).**

Table (2): Shows comparison between group A and group B as regards ECG findings

Group / ECG finding		Group A (CKD patients) N=45	Group B (HD patients) N=50	X^2 P
Normal	Count (Total=27)	14	13	**Pearson chi square** **1.456 0.384** **Likelihood ratio** **1.461 0.482** **Linear by linear association** **0.017 0.897**
	% within total	51.9%	48.1%	
	% within Group	31.1%	26.0%	
LVH	Count (Total=42)	17	25	
	% within total	40.5%	59.5%	
	% within Group	37.8%	50.0%	
IHD	Count (Total=26)	14	12	
	% within total	53.8%	46.2%	
	% within Group	31.1%	24.0%	

ECG=Electrocardiography, CKD=Chronic kidney disease, HD=Hemodialysis, LVH=Left ventricular hypertrophy, IHD=Ischemic heart disease.

***NB*:5 cases in Group A refused ECG, so, the number (N) is 45.**

Table 2 shows that, there is no difference between Group A and Group B as regards ECG findings even after use of many statistical types of chi square test (Pearson chi square test, likelihood ratio and linear by linear association) ***(p>0.05).***

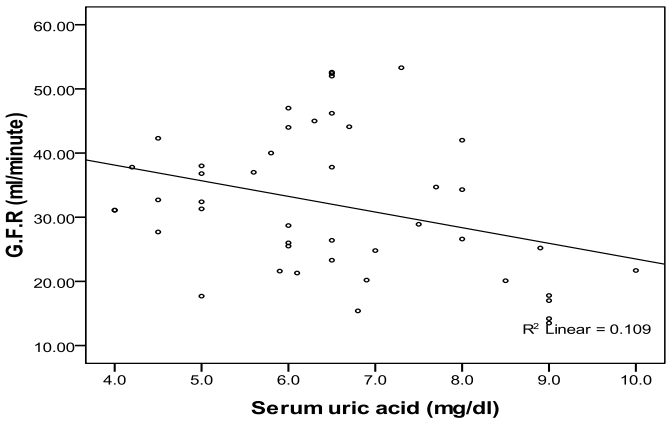

***Figure 1*: Correlation between serum uric acid and GFR**

Figure 1 shows that there is an inverse significant relationship between serum uric acid and eGFR ***(p<0.05).***

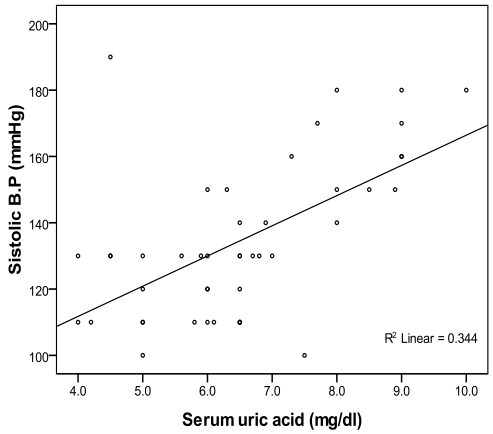

Figure 2: **Correlation between serum uric acid and SBP in Group A**

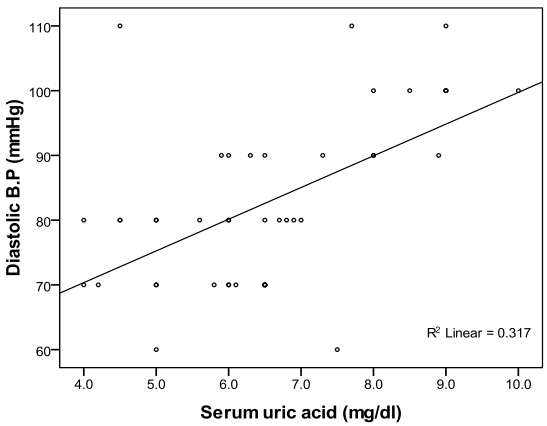

Figure 3: **Correlation between serum uric acid and DBP in Group A**

Figures 2 and 3 show highly significant correlations between serum uric acid and both systolic and diastolic blood pressures in Group A ***(p<0.01*** for both).

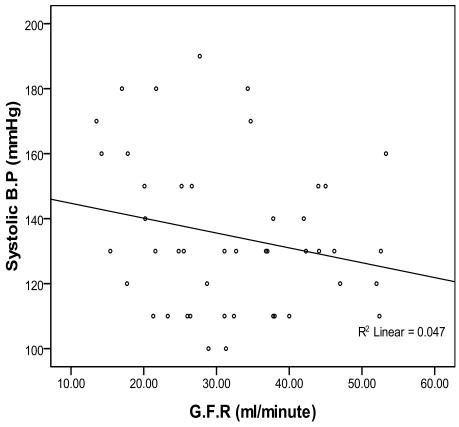

Figure 4: **Correlation between GFR andSBP in Group A**

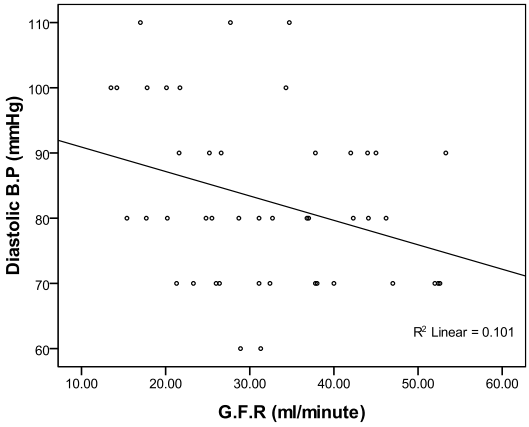

Figure 5: **Correlation between GFR and DBP in Group A**

Figure 4 shows a significant correlation between GFR and SBP ***(p<0.05)***while figure 5 shows a highly significant correlation between GFR and DBP ***(p<0.01***) in Group A.