A Preliminary Investigation of the Association between Serum Uric Acid and Impaired Renal Function

Yi-Cheng Chen, MD, PhD; Chien-Tien Su, MD; Sen-Te Wang, MD; Hsin-Dai Lee, MD; Shiyng-Yu Lin, MD

Background: Hemodialysis for end-stage renal disease (ESRD) incurs huge medical costs in Taiwan. We set out to determine if it is possible to help control chronic renal disease with early treatment of hyperuricemia.

Methods: Data from Taipei Medical University Hospital (TMUH) health center from January 2004 to December 2006 were analyzed to correlate renal function and blood uric acid concentration. Patients were divided into 5 groups according to their serum uric acid concentration (< 4; 4~5.9; 6~7.9; 8~9.9, and > 10 mg/dl). According to our laboratory data, elevated serum creatinine levels (> 1.3 mg/dL) indicated impaired renal function.

Results: In total, there were 5722 patients, including 2816 (49.2%) men and 2906 (50.8%) women, with a median age of 67. Impaired renal function was noted in 307 (5.4%) cases. Serum uric acid was significantly correlated with blood urea nitrogen and serum creatinine. Groups with a higher serum uric acid level had an increased risk of impaired renal function.

Conclusion: Our purpose in this preliminary observation was to try to define a starting point for the early control of serum uric acid, in order to avoid the development of impaired renal function. We found that serum uric acid level to < 6 mg/dl seemed to be associated with less renal function impairment.

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Key words: uric acid, blood urea nitrogen (BUN), serum creatinine, impaired renal function

Taiwan is a leading area utilizing hemodialysis for end-stage renal disease (ESRD), and this incurs huge medical costs. Efforts to prevent the development or progression of chronic renal disease are thus of great importance. Reports show a nearly invariable occurrence of hyperuricemia in chronic kidney disease in humans and a high frequency of chronic renal impairment in patients who have gout. We set out to determine if it is possible to contribute to the control of chronic renal disease by early treatment of hyperuricemia.[1,2]

While experimenting on Sprague-Dawley rats, we discovered that mild oxonate-induced increases in serum urate levels resulted in glomerular hypertension, hypertrophy and, ultimately, sclerosis; renin-dependent systemic hypertension and afferent renal artery arteriosclerosis; and interstitial renal inflammation, terminating in fibrosis[3] All of these changes

From the Department of Family Medicine, Taipei Medical University Hospital, Taipei, Taiwan.
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Correspondence to: Dr. Shiyng-Yu Lin, Department of Family Medicine, Taipei Medical University Hospital. No. 252, Wusing St., Sinyi District, Taipei City 110, Taiwan, (R.O.C.) Tel.: 886-2-27372181 ext. 1111; Fax: 886-2-28310123;
E-mail: daleslin@hotmail.com

occur at high but sub-saturated urate levels and are independent of urate crystal deposition.[4] A role for increased urate levels in worsening structural and functional renal disease has also been demonstrated in cyclosporine-induced and remnant kidney models of chronic kidney disease in rats.[5]

In epidemiologic studies, urate levels were reported to be correlated with the development of chronic renal insufficiency in patients with hypertension and impaired renal function.[6-8] Therefore, we analyzed the database of Taipei Medical University Hospital (TMUH) health center to examine the relationship between uric acid and renal function. Hopefully a strategy for controlling serum uric acid can prevent damage to renal function.

METHODS

We collected data on adult residents aged 40 years or older who lived in Taipei City and visited a TMUH health center from January 2004 to December 2006. Data collected included gender, age, body weight, blood pressure, history of smoking and drinking alcohol, blood glucose, triglycerides, cholesterol, blood urea nitrogen, serum creatinine and uric acid concentration.

We divided the patients into 5 groups according to the serum uric acid concentration (< 4; 4~5.9; 6~7.9; 8~9.9, and > 10 mg/dl). We tried to determine if a lower uric acid level, correlated to better renal function, to provide referential data for early control of serum uric acid.

According to the Taiwan Society of Nephrology (T.S.N.) for chronic kidney disease (CKD) prevention, early impaired renal function is defined as a glomerular filtration rate (GFR) less than 90 ml/min. Calculation of the modification of diet in renal disease (MDRD)-GFR (Stephen Z Fadem M.D. FACP, FASN) shows that an MDRD less than 60 is equivalent to a GFR less than 90 ml/min in a 67 year-old man with a serum creatinine level of 1.3 mg/dl (women meet a stricter serum creatinine level of 0.9 mg/dl). Therefore, we considered elevated serum creatinine levels (> 1.3 mg/dl) as impaired renal function (IRF) in this preliminary observation.

Statistical analysis was performed using the SAS statistical package (version 9.0). Student's t-test or χ^2 test was used to compare the differences in clinical indices between subjects with IRF and healthy controls (Table 1). A multiple logistic regression model was used to estimate age- and sex-adjusted odds ratios (OR) and 95% confidence intervals (CI) of IRF associated with clinical indices and life-related factors. We analyzed the significant variables in Table 1 through stepwise logistic regression and adjusted the potential confounders in the following analyses. Multiple linear regression was used to elucidate the relationship between uric acid, BUN and creatinine levels, after adjustment for potential confounders (Table 2). Finally, we used multiple logistic regression models to estimate the OR of IRF associated with uric acid levels (Table 3).

A p value of 0.05 (two-sided) was considered significant.

RESULTS

In total, 5722 cases, including 2816 (49.2%) men and 2906 (50.8%) women, with a median age of 67 (range, 40~95) years were examined. IRF was noted in 307 (5.4%) cases. (Table 1) Serum uric acid was significantly associated with blood urea nitrogen and serum creatinine (with regression coefficients of 0.73 and 0.05, respectively, after adjusting for age, gender, and leukocyte, globulin and triglyceride levels in multivariate linear regression; $p < 0.0001$). (Table 2)

Furthermore when compared with the group with the lowest serum uric acid, the risk of IRF in the group with a uric acid level (UA) of 4~5.9 mg/dl was 1.43-fold (95% CI = 0.61~3.36) higher; in the 6~7.9 mg/dl group 2.38-fold (95% CI = 1.10~5.90) higher; in the 8~9.9 mg/dl group 6.73-fold (95% CI = 3.26~18.13) higher; and in the ≥ 10 mg/dl group 19.05-fold (95% CI = 7.35~50.70) higher. (Table 3). This shows that groups with a higher serum uric acid level had an increased risk of impaired renal function.

DISCUSSION

Uric acid is the final product of purine metabolism in human beings.[9] For years, hyperuricemia has been identified with or thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities.[10-14]

Blood uric acid levels are a function of the bal-

Table 1. Comparison of Clinical Indices and Life-related Factors between IRF Subjects and Healthy Controls

Variables	IRF (Mean ± S.E) n = 307	Non-IRF (Mean ± S.E) n = 5415	Mean difference (95% CI)	OR* (95% CI)	*p* value
Uric acid	7.48 ± 0.11	5.87 ± 0.02	–1.61 (–1.79, –1.43)		
BUN	24.84 ± 0.68	15.28 ± 0.06	–9.55 (–10.14, –8.97)		
Creatinine	2.15 ± 0.09	0.87 ± 0.01	–1.28 (–1.33, –1.23)		
Age	77.23 ± 0.54	66.75 ± 0.17	–10.48 (-11.93, –9.02)	1.07 (1.06–1.09)	<. 01
Sex					
Female	51 (16.61)	2855 (52.72)		1.00	< .01
Male	256 (83.39)	2560 (47.28)		4.11 (3.01–5.60)	
SBP	134 ± 1.23	126.75 ± 0.35	–7.26 (–10.22, –4.29)	1.01 (1.00–1.01)	0.03
DBP	78.63 ± 0.611	77.66 ± 0.28	–0.97 (–3.33, 1.39)	1.00 (1.00–1.01)	0.69
Leukocytes	6.44 ± 0.10	6.03 ± 0.029	–0.41 (–0.65, –0.17)	1.07 (1.03–1.12)	< .01
Erythrocytes	18.39 ± 14.17	4.75 ± 0.13	–13.64 (–20.33, –6.95)	1.00 (1.00–1.01)	0.39
Platelets	211.7 ± 3.73	236.18 ± 1.14	24.46 (14.89, 34.02)	1.00 (1.00–1.01)	0.50
Hemoglobin	14.26 ± 0.74	14.64 ± 0.19	0.38 (–1.19, 1.95)	0.99 (0.98–1.01)	0.51
Albumin	4.19 ± 0.02	4.33 ± 0.01	0.13 (0.10, 0.17)	0.55 (0.40–0.77)	< .01
Globulin	3.12 ± 0.03	2.98 ± 0.01	–0.14 (–0.19, –0.09)	1.82 (1.43–2.32)	< .01
Cholesterol	185.83 ± 2.04	194.13 ± 0.49	8.31 (4.19, 12.42)	1.00 (1.00–1.01)	0.83
Triglycerides	138.29 ± 5.50	122.40 ± 1.27	–15.88 (–26.65, –5.11)	1.00 (1.00–1.01)	< .01
SGOT	25.32 ± 1.41	23.72 ± 0.23	–1.59 (–3.59, 0.40)	1.00 (1.00–1.01)	0.30
SGPT	23.14 ± 2.46	23.92 ± 0.38	0.78 (–2.58, 4.15)	1.00 91.00–1.01)	0.65
Blood glucose	114 ± 2.05	108.52 ± 0.49	–5.48 (–9.59, –1.37)	1.00 (1.00–1.01)	0.12
Smoking					
Never	276 (89.90)	5044 (93.15)		1.00	0.15
Current	31 (10.10)	371 (6.85)		1.34 (0.90–2.01)	
Drinking					
Never	304 (99.90)	5311 (98.08)		1.00	0.07
Current	3 (0.98)	104 (1.92)		0.33 (0.10–1.08)	

Abbreviations: IRF: impaired renal function; BUN: blood urea nitrogen; SBP: systolic blood pressure; DBP: diastolic blood pressure; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; *: Adjusted by age and sex.

Table 2. Multiple Liner Regression Analyses of Uric Acid, BUN and Creatinine Levels

Dependent variables	Regression coefficients* (95% CI)	*p* value
BUN	0.73 (0.64-0.82)	< .01
Creatinine	0.06 (0.05-0.07)	< .01

*: Adjusted by age, sex, and leukocyte, globulin and triglyceride levels.

Table 3. Multivariate-Adjusted Odds Ratios for IRF with Regard to Uric Acid Levels

Uric acid levels	No. with IRF/	without IRF OR* (95% CI)	*p* value
< 4	6/456	1.00†	
4-5.9	67/2549	1.43 (0.61-3.37)	0.41
6-7.9	123/1943	2.38 (1.03-5.54)	0.04
8-9.9	85/406	6.73 (2.85-15.91)	< .01
≥ 10	26/61	19.05 (7.13-50.89)	< .01

*: Adjusted by age, sex, and leukocyte, globulin and triglyceride levels; †: trend *p* value < 0.001 IRF: impaired renal function.

ance between the breakdown of purines and the rate of uric acid excretion.[9] Theoretically, alterations in this balance may account for hyperuricemia, although clinically defective elimination accounts for most cases of hyperuricemia.[15]

Animal models demonstrated renal pathologic findings as described earlier, with increased serum urate levels in Sprague-Dawley rats, which resulted in glomerular hypertension, hypertrophy, and, ultimately, sclerosis; renin-dependent systemic hypertension; afferent arteriolosclerosis; and interstitial renal inflammation terminating in fibrosis.[3] Also in cyclosporine-induced and remnant kidney models of chronic kidney disease in rats, worsening structural and functional renal disease was accompanied by increased urate levels.[5] Several genetic causes of renal disease are associated with hyperuricemia and gout. Most prominently, medullary cystic kidney disease type 2 (MCKD2) and the allelic disorder, familial juvenile hyperuricemic nephropathy (FJHN), are characterized by a reduced fractional excretion of uric acid, progressive renal dysfunction, frequent hyperuricemia,[16,17] and a high incidence of early-onset gout. This disorder is primarily caused by mutations in uromodulin or Tamm-Horsfall glycoprotein,[17] a glycosyl-phosphatidylinositol-anchored membrane protein with restricted expression at the luminal membrane of the thick ascending limb and distal convoluted tubule. Altered biosynthesis results in markedly reduced uromodulin excretion and intracellular aggregation within the distal nephron.[17] Presumably, hyperuricemia in these patients is secondary to renal tubular dysfunction, hypovolemia, and secondary neurohumoral activation of the renin-angiotensin- aldosterone axis or other mediators. Hyperuricemic renal disease has also been reported in a group with mutations in the hepatocyte nuclear factor-1b (HNF-1b) transcription factor.[18,19] Mutations in HNF-1b are associated with a spectrum of cystic, dysplastic, and developmental abnormalities of the kidney.[18] The clinical scenarios under which hyperuricemia can be considered symptomatic are gout, uric acid stones, and uric acid nephropathy. But in the US, the prevalence rate of asymptomatic hyperuricemia in the general population is estimated to be 2%~13%. Internationally, a Japanese study using their database to ascertain 10-year trends in the prevalence of hyperuricemia concluded that the prevalence of hyperuricemia in the overall study population increased during the 10-year follow-up.[15] When stratified by age, the prevalence increased among groups older than 65 years in both genders. In those younger than 65 years, men had a prevalence 4 times higher than women, but in those older than 65 years, the gender gap narrowed to 1:3 (female-to-male ratio) with gout and/or hyperuricemia.[20] By that time, most patients with asymptomatic hyperuricemia never develop gout or stones.[10] Treatment for asymptomatic hyperuricemia carries some risk. It is considered neither beneficial nor cost-effective, and generally is not recommended.[11-14] The exception to this is in an oncologic setting in which patients receiving cytolytic treatment may be treated prophylactically to prevent acute uric acid nephropathy. On the other hand, based on our preliminary data in this study, we found that higher serum uric acid levels were associated with an increased risk of impaired renal function. In our study, controlling the serum uric acid level to < 6 mg/dl seemed to be of help in preventing the development of renal disease. Of course, this limited renal function evaluation is a preliminary observation, and there is still a long way to go to determine firm principles for early control of serum uric acid. To make this result more reliable, we should add more parameters to evaluate renal function impairment. Fortunately, this observation still showed us that we are on the right track, and it is possible to control the level (< 6 mg/dl) of serum uric acid.

Conclusions

Our purpose in this preliminary observation was to provide referential data to define a starting point for the early control of serum uric acid, in order to avoid developing renal disease. We found that the serum uric acid level to < 6 mg/dl seemed to be associated with less renal function impairment. In future study, we will add more parameters such as urine microalbumin/creatinine for evaluating the renal condition, which can more exactly reflect the correlation between uric acid and renal function.

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血液中尿酸值和腎功能相關現象的初步觀察

陳怡誠 蘇千田 王森德 李欣岱 林神佑

背 景： 台灣因慢性腎病洗腎的醫療負擔花費不少社會成本，如何能預防慢性腎病的發生或減緩病情惡化的速度相當重要。動物實驗及流行病學文獻已報告高尿酸血症和慢性腎病有關，但從臨床醫療的立場來看，對於血中尿酸值的控制一直沒有明確的界線。基於上述原因，我們希望能找到一個有實證數據作依據的治療準則，以達到預防慢性腎病發展的目的。

方 法： 從 2004 年到 2006 年北醫健檢中心的數據，將 40 歲以上的人依血中尿酸值的高低分爲 5 組，將血清肌酸酐值大於 1.3 mg/dl 者視爲腎功能異常，分析各組腎功能異常之情形。

結 果： 總共 5722 人 (男性 2816 人；女性 2906 人)，腎功能異常的有 307 人 (5.4%)。血中尿酸值和血尿素氮，血清肌酐酸均有正相關。以尿酸值小於 4 mg/dL 的組別爲基準，計算發生腎功能異常的危險性。結果血中尿酸值高的組別，發生腎功能異常的危險性較高。而尿酸值在 4~6 mg/dl 的組別和基準組無差異。

結 論： 本研究之目的是希望能找到一個臨床上對控制血中尿酸值的準則，以預防發展成慢性腎病。從我們的經驗顯示，控制血中尿酸值小於 6 mg/dl，發生腎功能異常的危險性較低。當然人體尿酸的代謝和許多因素有關，而影響腎功能的變數也無法一概而論。本研究僅從結果來分析高尿酸血症和腎功能異常的相互關係，希望從繁瑣的理論中，找出臨床上簡單易用且有數據支持的準則。本研究僅爲開端，我們將加強對定義腎功能異常之證據，更進一步分析其他相關因素，期待提供站在健康管理第一線的醫療人員有用的資訊。

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台北醫學大學附設醫院 家庭醫學科
受文日期：民國97年1月16日；接受刊載：民國97年4月3日
通訊作者：林神佑醫師，台北醫學大學附設醫院 家庭醫學科。台北市110信義區吳興街252號。Tel.: (02)27372181轉1111; Fax: (02)28310123; E-mail: daleslin@hotmail.com