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Research Article

Uric Acid Level as a Risk Marker for Chronic Kidney Disease: Data Analysis of Health Examinations

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Abstract: This study investigated uric acid levels as a risk marker for chronic kidney disease (CKD).This cross-sectional study focused on the 9,450 persons who attended the free health check at a hospital in Kaohsiung, Taiwan between July 2005 and July 2011. CKD was divided into non-CKD, CKD stages 1-2, and CKD stages 3-5. The 2002 National Kidney Foundation kidney disease outcomes quality initiative (K/DOQI) was used as the standard for diagnosis. Multiple logistic regression analysis was used to examine the influence of uric acid levels on CKD. The ratio of advanced stage diagnoses increased as uric acid levels increased; the results for CKD stages 3-5 were more significant. Multiple logistic regression analysis indicated that in models 1, 2, and 3, as uric acid levels increased, the risk for CKD stages 1-2 and stages 3-5 increased. This increased risk was more significant for CKD stages 3-5.The amount of kidney damage caused by CKD increases as uric acid levels increase. While controlling all other risk factors, uric acid can be used as an independent predictor for CKD.
Keywords: Chronic kidney disease, uric acid, **g**lomerular filtration rate, health examination

INTRODUCTION

Past epidemiological studies and trials have indicated that serum uric acid is correlated with obesity, diabetes, hypertension, cardiovascular disease, and chronic kidney disease (CKD) [1-5], and increases the risk for metabolic syndrome [6-8]. In many countries, diabetic kidney disease (DKD) is a major cause of end-stage renal disease (ESRD) and is considered a worldwide burden. Uric acid (UA) has been found to be linked to DKD incidence and progression [9,10]. One study in a Chinese Population concluded that hyperuricaemia is a risk factor for DKD [11].

The key to preventing CKD is early detection and early treatment. If kidney disease is left unchecked, it can lead to declining kidney function and the inability to continue a healthy life [12]. Patients with more severe kidney disease require dialysis or transplants which are hazards to health in and of themselves. However, the development of CKD can be slowed or even prevented through conventional testing and treatments. This can also reduce the risk of comorbidities and cardiovascular disease and improve survival rate and quality of life [13]. A recent improvement in the detection of early stage CKD is the use of estimated Glomerular Filtration Rate (eGFR) rather than serum creatinine during diagnosis. The new kidney disease outcomes quality initiative (K/DOQI) guideline also uses eGFR in its definition and staging of CKD to help epidemiological screening and clinical treatment. This novel concept is already universally used within the field of nephrology [14].

The aging population and increased incidences of obesity, diabetes, hypertension, and other chronic diseases have contributed to the increase in kidney disease. As some medications are nephrotoxic, inappropriate medication use in Taiwan also directly damages kidney function. In addition, patients with chronic diseases may take drugs, herbs, or other supplements that are advertized to cure their disease that actually exacerbate their condition and hasten the development of kidney disease caused by hypertension or diabetes. CKD also leads to an increased risk of mortality, cardiovascular disease, and progression to renal failure [15-18]. While the high incidence and prevelance of ESRD in Taiwan is a pressing issue, the prevelance of CKD, a precursor to ESRD, is much higher.

This study investigated UA levels as a risk marker for CKD to serve as a reference for the treatment of CKD.

METHODS

This cross-sectional study focused on the 9,450 adults aged 40 years and older who attended the free health check at a hospital in Kaohsiung, Taiwan between July 1, 2005 and July 31, 2011. A total of 12,583 people received health checks; the effective sample was 9,450 after removing those who received multiple health checks and those with incomplete physiology, blood chemistry evaluations.

The physical examination included the following: blood pressure and anthropometric measurements, including height, weight, and body mass index (BMI). Height was measured to the nearest 0.1 cm, without shoes, using a stadiometer. Weight was measured in light clothing, without shoes, using a beam balance scale, and was recorded to the nearest 0.1kg. BMI was calculated as weight (kg) divided by height^2 (m^2). Well-trained nurses measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) two times in the left arm of seated participants according to a standardized protocol. A third BP measurement was made if the first two BP readings differed by more than 10 mm Hg. The average of the two closest readings was calculated to determine the reported BP for each participant.

Definition of terms: (1) Definition of CKD: In the present study, the GFR was estimated using the Modification of Diet in Renal Disease (MDRD), and CKD was grouped into 5 stages based on the categorization of CKD by the National Kidney Foundation, Inc.: a patient whose eGFR ≧90 ml/min/1.73m^2 with proteinuria was in stage 1; those with eGFR ≧60-89 ml/min/1.73m^2 with proteinuria were in stage 2; those with eGFR ≧30-59 ml/min/1.73m^2 were in stage 3; those with eGFR ≧15-29ml/min/1.73m^2 were in stage 4; those with eGFR <15ml/min/1.73m^2 were in stage 5. (2) In order to understood the current international classification of UA as a criterion of elevated UA, the present study classified the serum UA level into (A) UA >7.0mg/dL for males and UA >6.0mg/dL for females [19,20]; (B) 3 subgroups in light of the concentration of UA: (a) UA <7mg/dL, (b) 7mg/dL ≦UA <9mg/dL, (c) UA ≧9mg/dL [21]. (C) 4 subgroups among males: (a) UA <5mg/dL, (b) 5mg/dL ≦UA <6mg/dL, (c) 6 mg/dL ≦UA <7mg/dL, and (d) UA≧7mg/dL. In females: (a) UA <4mg/dL, (b) 4mg/dL ≦UA<5mg/dL, (c) 5mg/dL ≦ UA< 6mg/dL, and (d) UA ≧6mg/dL [22].

The Meiho University Institutional Review Board approved this study prior to data collection. SPSS for Windows release 17.0 was used for data analysis; significance levels were set at α= .05. Chi-square tests and multiple logistic regression analysis were used to examine the correlations between UA and CKD stages.

RESULTS

The results of the demographics, lifestyles, and CKD staging (non-CKD, stages 1-2, and stages 3-5) analysis indicated that males, aged 65 and above, without the habits of a daily consumption of vegetables and fruits have an increasing prevalence of CKD. Those who exercise and smoke have a higher prevalence of CKD (Table 1).

Table-1: Analysis of demographics, lifestyles, and CKD (n=9450)

Variable	non CKD(n=6757)		stage1-2(n=1104)		stage3-5(n=1589)		P value
	Number	Percentage	Number	Percentage	Number	Percentage	
Gender							<.001
Male	2838	68.2	539	12.9	786	18.9	
Female	3919	74.1	565	10.7	803	15.2	
Age							<.001
40-64 Years	4772	82.7	616	10.7	382	6.6	
Above 65	1985	53.9	488	18.3	1207	32.8	
Daily Vegetable and Fruit[a]							.025
Yes	4548	72.4	717	11.4	1018	16.2	
No	2209	69.8	387	12.2	571	18.0	
Exercise [b]							<.001
No	4677	72.5	754	11.7	1019	15.8	
3-5 times a week	2080	69.3	350	11.7	570	19.0	
Smoking [c]							<.001
No	5808	71.2	923	11.3	1423	17.5	
Yes	949	73.2	181	14.0	166	12.8	

[a] Daily vegetable and fruit intake: 3 kinds of vegetables, 2 kinds of fruit.
[b] Exercise: More than 30 minutes each time.

[c] Smoking: Currently smoking.

Table 2 indicates that while total cholesterol was not significant, all other metabolic syndrome and its components abnormalities prevalence increased along with more advanced stages of CKD ($p<0.001$). Table 3 compares UA levels and CKD staging; the results showed that regardless of whether UA was divided into two, three, or four subgroups, an increasing trend could be seen in CKD as UA levels increased; particularly significant differences were found for CKD stages 3-5 ($p<0.001$). After adjusted for age, gender, exercise habits, smoking habits, daily fruit and vegetable intake, and metabolic syndrome, multiple logistic regression analysis results indicated that UA subgroups in models 1, 2, and 3 saw increased risk for CKD stages 1-2 and stages 3-5 with increases in UA levels; this increase was more significant for CKD stages 3-5 (Table 4).

Table-2: Analysis of physiology, blood chemistry, and CKD (n=9450)

Variable	non CKD(n=6757)		stage1-2(n=1104)		stage3-(n=1589)		P value
	Number	Percentage	Number	Percentage	Number	Percentage	
BMI							<.001
18.5≦ BMI <26.9 Kg/m^2	5322	73.0	785	10.8	1182	16.2	
BMI≧27kg/m^2	1435	66.4	319	14.8	407	18.8	
Blood Pressure Elevation[d]							<.001
Normal	2693	82.5	219	6.7	354	10.8	
Abnormal (≧130/85mmHg)	4064	65.7	885	14.3	1235	20.0	
Cholesterol							.151
Normal	3613	71.1	580	11.4	888	17.5	
Abnormal (≧200mg/dL)	3144	72.0	524	12.0	701	16.0	
Triglyceride							<.001
Normal	5049	73.7	735	10.7	1065	15.5	
Abnormal (≧150mg/dL)	1708	65.7	369	14.2	524	20.1	
Blood Sugar Elevation[e]							<.001
Normal	3354	77.8	399	9.3	557	12.9	
Abnormal (≧100mg/dL)	3403	66.2	705	13.7	1032	20.1	
Metabolic Syndrome							<.001
No (Less than <3 items of abnormality)	4340	75.5	558	9.7	854	14.8	
Yes (More than≧3 items of abnormality)	2417	65.4	546	14.8	735	19.9	

[d] Blood pressure elevation≧130/85mmHg or currently taking antihypertensive drug.
[e] Blood sugar elevation≧100mg/dl or currently taking oral hypoglycemic agent.

Table-3: Analysis the difference of uric acid level and CKD (n=9450)

Variable	non CKD(n=6757)		stage1-2(n=1104)		stage3-5(n=1589)		P value
	Number	Percentage	Number	Percentage	Number	Percentage	
High UA							<.001
Normal	5089	79.4	732	11.4	588	9.2	
Abnormal (Male >7, Female >6mg/dL)	1668	54.9	372	12.2	1001	32.9	
Subgroup of UA[f]							<.001
tertile 1	5510	77.8	832	11.8	738	10.4	
tertile 2	1099	57.5	227	11.9	584	30.6	
tertile 3	148	32.2	45	9.8	267	58.0	
Subgroup of UA[g]							<.001
quartile 1	1036	83.7	131	10.6	71	5.7	
quartile 2	1908	81.5	262	11.2	172	7.3	
quartile 3	1976	76.7	301	11.7	300	11.6	
quartile 4	1837	55.8	410	12.5	1046	31.8	

[f] Subgroups of UA: tertile1: UA <7mg/dL; tertile2: 7mg/dL≦UA <9mg/ dL; tertile3: UA≧9mg/dL.
[g] Subgroups of UA:
quartile1: Male UA <5mg/dL, Female UA <4mg/dL;
quartile2: Male 5mg/dL≦UA <6mg/dL, Female 4mg/dL≦UA <5mg/dL;

quartile3: Male 6 mg/dL≦UA＜7mg/dL,Female 5mg/dL≦UA＜6mg/dL;
quartile4: Male UA≧7mg/dL, Female UA≧6mg/dL.

Table-4: Multiple logistic regression analysis of the association between uric acid and predicted the risk for CKD

Item		
	CKD stage 1-2 OR (95% CI)	CKD stage 3-5 OR (95% CI)
Model 1		
UA	1.38(1.20-1.59)	5.17(4.55-5.87)
Model 2		
tertile 2 [a]	1.18(1.00-1.40)	4.30(3.72-4.98)
tertile 3 [a]	1.67(1.18-2.36)	15.13(11.81-19.37)
Model 3		
quartile 2 [b]	1.11(0.86-1.39)	1.41(1.05-1.90)
quartile 3 [b]	1.19(0. 95-1.48)	2.29(1.81-3.16)
quartile 4 [b]	1.58(1.27-1.96)	8.87(6.81-11.56)

Note 1: Depended variables included non CKD, CKD stages 1-2, and CKD stages 3-5; using the non CKD group as the reference group.
Note 2: The multiple logistic regression models included the following variables: age, gender, uric acid, exercise habits, smoking habits, daily fruit and vegetable intake, and metabolic syndrome.

[a]Uric acid subgroups: tertile1:UA < 7mg/dL; tertile 2:7mg/dL≦UA < 9mg/ dL; tertile 3:UA≧9mg/dL.

[b]Uric acid subgroups:

quartile 1: male UA < 5mg/dL ，female UA < 4mg/dL.

quartile 2:male 5mg/dL≦UA < 6mg/dL ，female 4mg/dL≦UA < 5mg/dL.

quartile3:male 6 mg/dL≦UA < 7mg/dL ，female 5mg/dL≦UA < 6mg/dL.

quartile 4:male UA≧7mg/dL ，female UA≧6mg/dL.

DISCUSSION

Age is a factor contributing to the development of CKD; the incidence of CKD increases as age increases. In this study, 32.8% of the participants aged over 65 had CKD stages 3-5, markedly higher than the 6.6% of participants aged 40-64. This is consistent with the results of Hemmelgarn, who noted that within a sample of 10,184 participants, kidney function decreased as age increased [23]. The results indicated that CKD stages 1-2 was more prevalent in smokers than non-smokers, yet CKD stages 3-5 were more prevalent in non-smokers than in those who smoked one pack of cigarettes per day (p<0.001). The causal relationship between CKD, smoking habits, and quitting smoking after diagnosis may be difficult to ascertain using a cross-sectional questionnaire. However, many studies have shown that nicotine damages endothelial cells and produces hydroxyl radicals, further deteriorating kidney function. Nicotine accumulates more in CKD patients than in healthy individuals, which further accelerates kidney damage. In a study including 2,310 participants aged 40 years and older, Zhang (2007) found that the kidney function in smokers was 1.56 times worse than that in healthy individuals [24]. Another study on diabetes patients concluded that smoking affects the glomerular structure and function and worsens this condition [25].

A prior study has shown that obesity causes a high glomerular filtration rate, adipose cells produce molecules that induce inflammation, and morbid obesity also increases renal blood flow, leading to kidney damage [26]. This study found that participants with a body mass index (BMI) ≥ 27 Kg/m^2 had significantly higher prevalences of CKD stages 1-2 and stages 3-5. This is consistent with previous studies that concluded a higher BMI increased the risks for CKD and ESRD [27, 28].

In this study, 33.8% of CKD patients had abnormal blood sugar levels; among which, a higher percentage of these patients were in stages 3-5 than stages 1-2 (20.1% vs. 12.9%). Nephropathy caused by diabetes is a leading cause of end stage renal failure. Studies focusing on diabetic CKD stage 5 patient information concluded that diabetics began dialysis treatments earlier than non-diabetics [9, 10] and that glycated hemoglobin should be kept under 7% in order to prevent blood sugar from further damaging kidney function.

This study also found that hypertension was associated with a higher risk of CKD (p<0.001). A higher percentage of hypertension was noted in CKD stages 3-5 than in CKD stages 1-2 (20.0% vs.14.3%); these percentages were both higher than the percentages for patients with normal blood pressure. Hypertension is the most prevalent comorbidity in individuals with CKD [29]. Past studies have indicated that increases in systolic pressure and diastolic pressure are strongly related to ESRD [30, 31]. Another study indicated a

strong correlation between higher pulse pressure and cardiovascular disease and a correlation between higher systolic and diastolic pressures and long-term dialysis [32]. Yet another study had similar findings, concluding that systolic pressure was a better predictor for kidney disease than diastolic pressure in individuals with type 2 diabetic nephropathy [33]. This study indicated that CKD stages 1-2 and stages 3-5 were significantly more prevalent in individuals with metabolic syndrome than those without; this finding was consistent with previous studies [34].

The majority of current studies focuses on UA levels as a risk factor for CKD and concludes that UA levels are correlated to CKD [21, 35]. Few studies divide UA levels into subgroups to investigate the influence on CKD stages. This study examined the relationship between UA levels and non-CKD, CKD stages 1-2, and CKD stages 3-5 groups. After adjusted for age, gender, exercise habits, smoking habits, daily fruit and vegetable intake, and metabolic syndrome, the results indicated that UA subgroups in models 1, 2, and 3 saw increased risks for CKD stages 1-2 and CKD stages 3-5 as UA levels increased; the increased risk for CKD stages 3-5 was particularly significant. This study was limited by the fact that the participants all came from the same region and all patient information was obtained from health checks provided by a single regional hospital; thus, the results may not be pertinent for all similar populations. In addition, some possible factors affecting CKD could not be collected. As this was a cross-sectional study, the causal relationships that may be inferred from the results are also limited. In conclusion, the prevalences of CKD stages 1-2 and CKD stages 3-5 in this study were 11.7% and 16.8%, respectively. A higher percentage of abnormal UA levels can be seen in patients with CKD stages 3-5. After controlling for other potential influencing factors of CKD, UA was still an independent predictor for CKD and as UA levels increased, the risk for CKD increased.

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