

Association of Renal Manifestations with Serum Uric Acid in Korean Adults with Normal Uric Acid Levels

Dong-Hyuk Jung¹, Yong-Jae Lee¹,
Hye-Ree Lee¹, Jung-Hyun Lee²,
and Jae-Yong Shim¹

Departments of Family Medicine¹, and Health Promotion Center², Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Received: 3 December 2009

Accepted: 3 August 2010

Address for Correspondence:

Jae-Yong Shim, M.D.

Department of Family Medicine, Yonsei University College of Medicine, 712 Eonju-ro, Dogok-dong, Gangnam-gu, Seoul 135-720, Korea

Tel: +82.2-2019-3482, Fax: +82.2-3463-3287

E-mail: hope@yumc.yonsei.ac.kr

Several studies have reported that hyperuricemia is associated with the development of hypertension and cardiovascular disease. Increasing evidences also suggest that hyperuricemia may have a pathogenic role in the progression of renal disease. Paradoxically, uric acid is also widely accepted to have antioxidant activity in experimental studies. We aimed to investigate the association between glomerular filtration rate (GFR) and uric acid in healthy individuals with a normal serum level of uric acid. We examined renal function determined by GFR and uric acid in 3,376 subjects (1,896 men; 1,480 women; aged 20–80 yr) who underwent medical examinations at Gangnam Severance Hospital from November 2006 to June 2007. Determinants for renal function and uric acid levels were also investigated. In both men and women, GFR was negatively correlated with systolic and diastolic blood pressures, fasting plasma glucose, total cholesterol, uric acid, log transformed C reactive protein, and log transformed triglycerides. In multivariate regression analysis, total uric acid was found to be an independent factor associated with estimated GFR in both men and women. This result suggests that uric acid appears to contribute to renal impairment in subjects with normal serum level of uric acid.

Key Words: Glomerular Filtration Rate; Uric Acid; Antioxidants

INTRODUCTION

Several studies have reported that hyperuricemia is associated with the development of hypertension and cardiovascular disease (1-3). In addition, epidemiological studies have shown an association between a high level of serum uric acid and increased vascular events and mortality in patients with hypertension (4).

More evidences also show that hyperuricemia may have a pathogenic role in the progression of renal disease (5). Iseki et al. (6) showed that an elevated serum uric acid level correlated with the development of renal insufficiency in individuals with normal kidney function. Paradoxically, it has been suggested that uric acid have antioxidant activity in experimental studies (7). In addition, it has been reported that uric acid administration to healthy volunteers increase their serum antioxidant capacity (8). Studies have shown that the relationship between serum uric acid and cardiovascular risk is J-shaped with a nadir in the second quintile (3, 9). This may reflect the association between low serum uric acid and low plasma antioxidant activity (10). There are also evidences showing that hyperuricemia seems to induce high blood pressure, renal afferent arteriopathy, a rise in glomerular hydrostatic pressure, and renal scarring (11). However, the relationship between the estimated glomerular filtration rate (eGFR) and serum uric acid has not been stud-

ied in people with normal serum levels of uric acid. Therefore, we aimed to investigate the association between eGFR and uric acid in a general population with physiological serum levels of uric acid.

MATERIALS AND METHODS

Study population

We studied adults who were between 20-80 yr old and visited Gangnam Severance Hospital for Preventive Medicine for a medical examination and health counseling. Cross-sectional surveys of adults listed on the electoral roll were undertaken from November 2006 to June 2007. This study is based on an analysis of the data from 2,170 males and 1,658 females at the time of their first survey. A total of 452 subjects (274 men, and 178 women) were excluded based on the following exclusion criteria: 14 subjects reported the current use of blood uric acid-lowering agents; 118 subjects had a history of cancer, ischemic heart disease, stroke, respiratory, renal, liver, or rheumatologic disease; 234 had high levels of uric acid level (≥ 7 mg/dL for men and ≥ 6 mg/dL for women) (12), and 86 had missing medical history, laboratory, or urinalysis data. Because some individuals were excluded for multiple reasons, the total number of eligible subjects for the study was 3,376 (1,896 men, and 1,480 women).

Data collection

Medical examinations were performed by trained medical staff according to a standardized procedure. Participants were asked about health-related behaviors, including cigarette smoking, alcohol consumption, and physical activity as well as current treatments for any type of disease. If subjects were receiving treatment, they were asked to provide the date of diagnosis of the disease and a list of medications being taken. Body weight and height were measured in light indoor clothing without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the ratio of weight (kg)/height (m²). After a 12-hr overnight fast, blood samples were obtained from each subject from the antecubital vein. Fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, high sensitivity-C reactive protein (CRP), and uric acid were measured using a Hitachi 7600-110 Chemistry analyzer (Hitachi, Tokyo, Japan). Kidney function was calculated using the Modification of Diet in Renal Disease 7 (MDRD7) equation: $GFR (mL/min \text{ per } 1.73 \text{ m}^2) = 170 \times (\text{serum creatinine})^{-0.9994} \times (\text{age})^{-0.176} \times (\text{BUN})^{-0.170} \times (\text{albumin})^{0.318} \times (0.762 \text{ if female})$ (13).

Urine protein was determined at each examination by a single uric stick semi-quantitative analysis (URiSCAN Urine Strip; YD Diagnostics, Yong-In, Korea). Dipstick urinalysis was conducted on fresh, midstream urine samples collected in the morning. The amount of urine protein was reported as absent, trace, 1+, 2+ 3+, or 4+. The results of trace, 1+, 2+, 3+, and 4+ correspond to protein levels of about 10, 30, 100, 300, and 1,000 mg/dL, respectively. Proteinuria was defined as grades of 1+ or above (14). Diabetes was defined as a self-reported history of the disease or a fasting plasma glucose level ≥ 126 mg/dL. Hypertension was defined as a self-reported history of the disorder, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg.

Statistical analysis

Clinical and chemical characteristics of the study population were summarized. All continuous variables are presented as means (SD) or medians (IQR), and the categorical variables are summarized as percentages in each group. Due to skewness, CRP was log transformed before statistical analyses. Pearson and Spearman rank correlation coefficients were determined for GFR vs age, BMI, cigarette smoking, regular exercise, systolic and diastolic blood pressure, plasma glucose, CRP, non HDL-cholesterol, proteinuria, hypertension, diabetes, and uric acid in men and women. To examine independent factors of GFR, multivariate linear regression analyses were performed. All analyses were conducted using SPSS statistical software (version 15.0).

Table 1. Characteristics of the study population*

	Men (n=1,896)	Women (n=1,480)
Age (yr)	46.5 (10.2)	45.4 (10.8)
Body mass index (kg/m ²)	24.6 (2.7)	22.8 (3.0)
Current smokers (%)	39.2	5.3
Regular exercise (%) [†]	64.6	48.7
Systolic blood pressure (mmHg)	125.8 (15.9)	119.7 (15.8)
Diastolic blood pressure (mmHg)	78.7 (10.2)	74.1 (9.9)
Fasting plasma glucose (mg/dL)	94.5 (19.6)	90.5 (18.2)
non HDL cholesterol (mg/dL)	132.7 (31.8)	123.8 (32.6)
CRP (mg/dL)	0.61 (0.34-1.26)	0.47 (0.26-1.05)
Proteinuria (1+<) (%) [‡]	4.6	1
Hypertension (%) [§]	14.1	9.7
Diabetes (%)	2.5	1.4
Uric Acid (mg/dL)	5.2 (1.0)	4.1 (0.8)
GFR (mL/min/1.73 m ²)	91.9 (14.3)	94.8 (16.0)

*Data are expressed as means (SD), medians (IQR), or percentages; [†]Regular exercise was defined as over 30 min of aerobic exercise at least twice per week; [‡]Proteinuria was defined as grades of 1+ or greater; [§]Hypertension was defined as a SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or a history of this disorder; ^{||}Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL, or a history of the disorder. CRP, high sensitivity-C reactive protein; GFR, glomerular filtration rate.

Table 2. Results of the multiple linear regression analysis to assess the relationship between GFR and clinical variables in men and women*

Variables	Men			Women		
	Parameter, β	SE	P value	Parameter, β	SE	P value
Age (yr)	-0.344	0.030	<0.001	0.062	0.042	0.136
BMI (kg/m ²)	0.037	0.104	0.721	-0.105	0.140	0.453
SBP (mmHg)	0.013	0.041	0.743	-0.086	0.054	0.111
DBP (mmHg)	-0.089	0.064	0.165	0.046	0.085	0.592
FPG (mg/dL)	-0.044	0.015	0.003	-0.008	0.023	0.736
Non HDL cholesterol (mg/dL)	-0.021	0.009	0.024	-0.027	0.013	0.036
Log CRP	-0.516	0.690	0.454	-1.375	0.943	0.145
Uric acid (mg/dL)	-4.998	0.298	<0.001	-6.118	0.479	<0.001
DM	-5.926	1.840	0.001	-4.962	3.352	0.139
HTN	0.949	0.863	0.272	2.687	1.434	0.061
Cigarette smoking	-1.927	0.596	0.001	-1.265	1.753	0.471
Proteinuria (1+<)	-1.858	1.372	0.176	7.702	5.339	0.149
Regular exercise	-0.170	0.614	0.782	-0.696	0.799	0.384

*Multivariate linear regression analysis included age, BMI, SBP, DBP, fasting plasma glucose, total cholesterol, HDL-cholesterol, log transformed triglycerides, log transformed CRP, current history of cigarette smoking, regular exercise, DM, hypertension, proteinuria, and uric acid as independent variables. GFR, glomerular filtration rate; BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; CRP, C reactive protein; DM, diabetes mellitus; HTN, hypertension; SE, standard error.

All statistical tests were 2-sided, and significance was determined at a *P* value <0.05.

Ethics statement

The study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University, College of Medicine in Seoul, Korea (3-2008-0174). Informed consent was exempted by the review board.

RESULTS

The data of 3,376 study participants are presented in Table 1. The average age was 46.5 yr for men, 45.4 yr for women, and the mean level of serum uric acid was 5.2 mg/dL for men and 4.1 mg/dL for women. Approximately 39.2% of men and 5.3% of women were current smokers, while 64.6% of men and 48.7% of women exercised regularly. The overall prevalence of diabetes was 2.5% for men and 1.4% for women.

In multivariate linear regression analysis, age, DM, cigarette smoking, fasting plasma glucose, non-HDL cholesterol, and uric acid were found to be independent variables that were significantly associated with GFR in men. Non HDL-cholesterol and uric acid were found to be independent variables associated with GFR in women (Table 2). Multiple stepwise regression models were used to evaluate the association of GFR with uric acid (Tables, 3, 4). The association of GFR with uric acid was negative after adjusting for age, DM, cigarette smoking, fasting plasma glucose and now HDL-cholesterol (Table 4).

Table 3. Factors affecting GFR as determined by multiple stepwise regression analysis in men and women*

Variables	Men			Women		
	Parameter, β	SE	<i>P</i> value	Parameter, β	SE	<i>P</i> value
Age (yr)	-0.334	0.028	<0.001	-0.035	0.036	0.328
Uric acid (mg/dL)	-5.672	0.273	<0.001	-6.528	0.439	<0.001

*A stepwise regression is allowed two variables to enter and remain; age and uric acid were the independent variables. GFR, glomerular filtration rate.

Table 4. Factors affecting GFR as determined by multiple stepwise regression analysis in men and women*

Variables	Men			Women		
	Parameter, β	SE	<i>P</i> value	Parameter, β	SE	<i>P</i> value
Age (yr)	-0.358	0.028	<0.001	0.025	0.036	0.499
FPG (mg/dL)	-0.052	0.015	<0.001	-0.020	0.022	0.355
Non HDL cholesterol (mg/dL)	-0.026	0.009	0.005	-0.037	0.012	0.003
Uric acid (mg/dL)	-5.490	0.275	<0.001	-6.237	0.453	<0.001
DM	-6.180	1.839	0.001	-4.942	3.322	0.137
Cigarette smoking	-1.919	0.595	0.001	-1.137	1.741	0.541

*A stepwise regression is allowed six variables to enter and remain; the independent variables were age, fasting plasma glucose, non HDL-cholesterol, current history of cigarette smoking, DM, and uric acid. GFR, glomerular filtration rate; FPG, fasting plasma glucose; DM, diabetes mellitus; SE, standard error.

It has been observed an increase in uric acid of 1 mg/dL is independently association with a decrease in GFR of about 5 mL/min/1.73 m² in men and about 6 mL/min/1.73 m² in women in Table 4.

DISCUSSION

In the present study, we found an association between increased uric acid levels and decreased GFR in Koreans with normal serum levels of uric acid. The liver produces uric acid by degrading dietary and endogenously-synthesized purine compounds. Uric acid is reabsorbed and excreted by the proximal tubular cells. Therefore, hyperuricemia might develop when the production of uric acid increases or the excretion of uric acid declines, or both (15). Several studies have shown that an increase in uric acid is associated with hypertension, cerebral vascular disease and chronic kidney disease (CKD) (2, 16, 17). Experimental animal studies and in vitro studies have identified the mechanisms in which elevated uric acid levels might cause nephrotoxicity. Afferent arteriopathy, mild tubulointerstitial fibrosis, glomerular hypertrophy, and glomerulosclerosis occur in hyperuricemic rats (18). However, despite several epidemiological, experimental, and prospective cohort studies, it is still controversial whether hyperuricemia can be considered to be a risk factor for the progression of CKD. Sturm et al. (19) reported that uric acid levels are not independent predictors of the progression of CKD. However, Iseki et al. (20) reported that a high level of serum uric acid was more predictive for the development of renal dysfunction than proteinuria. One of the reasons for the controversy over whether hyperuricemia is a risk factor for the progression of CKD is that uric acid may function as an antioxidant (21). Uric acid can chelate transition metals and can scavenge singlet oxygen and superoxide radicals (22). GFR has been suggested to be an indicator of early stages of kidney dysfunction (23). Therefore, we investigated the association between GFR and uric acid in a population with normal serum levels of uric acid. In multivariate linear regression analysis, age, cigarette smoking, fasting blood sugar, DM, and uric acid were independently and negatively associated with GFR in men, but not in women. Non-HDL cho-

lesterol and uric acid were independently and negatively associated with GFR in both men and women. Messerli et al. (24) reported that a decrease in GFR was correlated with an increase in uric acid in patients with hypertension. They argued this is because a low renal blood flow stimulates uric acid reabsorption. However, in our study, GFR was not significantly correlated with hypertension in either men or women. Galvan et al. reported that hyperuricemia develops frequently in subjects with insulin resistance, because insulin stimulates sodium and uric acid reabsorption in the proximal tubule (25). GFR was negatively associated with fasting blood sugar and DM in men, but not in women. The reason for this difference is unclear; however, the uricosuric effect of estrogen could be one possible reason for this difference (25). Recently, Chonchol et al. (26) reported that high uric acid levels are strongly associated with the risk of kidney disease progression and a decrease in estimated GFR based on a prospective community-based cardiovascular health study of 4,610 participants. However, it is also possible that hyperuricemia is just a bystander to kidney disease. One reason for this hypothesis is the fact that uric acid is excreted by the proximal tubular cells. When GFR decreases, both enteric excretion and fractional urinary excretion increase, but these processes do not fully compensate for the decrease in GFR, and hyperuricemia is induced (15). Therefore, CKD could be the cause of hyperuricemia. The other reason that hyperuricemia could just be a bystander to kidney disease is that uric acid is an antioxidant in the extracellular setting (22). Our study showed that an increase in uric acid of 1 mg/dL is independently associated with a GFR decrease of about 5 mL/min/1.73 m² in men and about 6 mL/min/1.73 m² in women. Although it is possible that a high level of uric acid could simply be a result of low GFR, several studies have provided evidences that uric acid might actually play a role in the development or progression of renal disease. Kang et al. (5) showed that uric acid induced renal hypertrophy, glomerulosclerosis and interstitial fibrosis in animal study. Yen et al. (27) reported that serum uric acid level was associated with a decline in renal function in a prospective study. Siu et al. (11) reported that allopurinol therapy was able to significantly decrease the probability of kidney function deterioration in a prospective trial of 54 hyperuricemic patients with CKD. Kanbay et al. (28) showed that treatment with allopurinol improved not only uric acid levels but also GFR in patients with normal renal function. These results suggest that uric acid might have play a pathologic role in kidney disease progression. Our findings are consistent with previous results showing a negative association between eGFR and the serum level of uric acid.

This study has several limitations. First, we used eGFR to assess renal function instead of directly measuring GFR. However, several organizations recommend the use of equations that estimate GFR to evaluate renal function in epidemiologic studies (29). Second, a dipstick can be inaccurate for detecting protein-

uria, because the number of false-positives can be increased by a comorbid illness in older people or by menstruation in women. However, in our study, we used this variable only as an adjustment variable. A third limitation was that the influence of hypertensive drugs as confounding variables was not examined. Diuretics such as thiazides increase serum uric acid by stimulating uric acid reabsorption in the proximal tubule (30). Last, this was a cross-sectional study; therefore, it is not clear whether the observed serum levels of uric acid contribute to the development of CKD. The potential therapeutic effects of lowering uric acid levels in CKD patients should be investigated in future prospective studies.

In conclusion, uric acid is independently and negatively associated with GFR in both men and women with normal serum levels of uric acid. This suggests that a high level of uric acid is a valuable predictor of a GFR decrease, and our findings have important clinical and public health implications.

REFERENCES

1. Niskanen LK, Laaksonen DE, Nyyssonen K, Alftan G, Lakka HM, Lakka TA, Salonen JT. *Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study.* *Arch Intern Med* 2004; 164: 1546-51.
2. Fang J, Alderman MH. *Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey.* *JAMA* 2000; 283: 2404-10.
3. Alderman MH, Cohen H, Madhavan S, Kivlighn S. *Serum uric acid and cardiovascular events in successfully treated hypertensive patients.* *Hypertension* 1999; 34: 144-50.
4. Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, Hofmann KP, Meyer J. *Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease.* *Am J Cardiol* 2002; 89: 12-7.
5. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. *A role for uric acid in the progression of renal disease.* *J Am Soc Nephrol* 2002; 13: 2888-97.
6. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. *Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort.* *Am J Kidney Dis* 2004; 44: 642-50.
7. Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P. *Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid.* *Biochem J* 1986; 235: 747-54.
8. Waring WS, Webb DJ, Maxwell SR. *Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers.* *J Cardiovasc Pharmacol* 2001; 38: 365-71.
9. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW, Applegate WB. *Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP).* *J Hypertens* 2000; 18: 1149-54.
10. Dawson J, Quinn T, Walters M. *Uric acid reduction: a new paradigm in the management of cardiovascular risk?* *Curr Med Chem* 2007; 14: 1879-86.
11. Siu YP, Leung KT, Tong MK, Kwan TH. *Use of allopurinol in slowing the*

- progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006; 47: 51-9.
12. Feig DI, Kang DH, Johnson RJ. *Uric acid and cardiovascular risk. N Engl J Med* 2008; 359: 1811-21.
 13. Poge U, Gerhardt T, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP. *MDRD equations for estimation of GFR in renal transplant recipients. Am J Transplant* 2005; 5: 1306-11.
 14. Ryu S, Chang Y, Kim DI, Kim WS, Suh BS. *gamma-Glutamyltransferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. Clin Chem* 2007; 53: 71-7.
 15. Vaziri ND, Freel RW, Hatch M. *Effect of chronic experimental renal insufficiency on urate metabolism. J Am Soc Nephrol* 1995; 6: 1313-7.
 16. Madsen TE, Muhlestein JB, Carlquist JF, Horne BD, Bair TL, Jackson JD, Lappe JM, Pearson RR, Anderson JL. *Serum uric acid independently predicts mortality in patients with significant, angiographically defined coronary disease. Am J Nephrol* 2005; 25: 45-9.
 17. Verdecchia P, Schillaci G, Reboldi G, Santeusano F, Porcellati C, Brunetti P. *Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension* 2000; 36: 1072-8.
 18. Sanchez-Lozada LG, Tapia E, Avila-Casado C, Soto V, Franco M, Santamaria J, Nakagawa T, Rodriguez-Iturbe B, Johnson RJ, Herrera-Acosta J. *Mild hyperuricemia induces glomerular hypertension in normal rats. Am J Physiol Renal Physiol* 2002; 283: F1105-10.
 19. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F; MMKD Study Group. *Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. Exp Gerontol* 2008; 43: 347-52.
 20. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. *Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res* 2001; 24: 691-7.
 21. Euser SM, Hofman A, Westendorp RG, Breteler MM. *Serum uric acid and cognitive function and dementia. Brain* 2009; 132: 377-82.
 22. Ames BN, Cathcart R, Schwiers E, Hochstein P. *Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA* 1981; 78: 6858-62.
 23. Cirillo M, Del Giudice L, Bilancio G, Franzese MD, Chiricone D, De Santo NG. *[Early detection of chronic kidney disease: epidemiological data on renal dysfunction.]. G Ital Nefrol* 2008; 25: 690-3.
 24. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. *Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med* 1980; 93: 817-21.
 25. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E. *Effect of insulin on uric acid excretion in humans. Am J Physiol* 1995; 268: E1-5.
 26. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. *Relationship of uric acid with progression of kidney disease. Am J Kidney Dis* 2007; 50: 239-47.
 27. Yen CJ, Chiang CK, Ho LC, Hsu SH, Hung KY, Wu KD, Tsai TJ. *Hyperuricemia associated with rapid renal function decline in elderly Taiwanese subjects. J Formos Med Assoc* 2009; 108: 921-8.
 28. Kanbay M, Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, Uz E, Akcay A, Yigitoglu R, Covic A. *Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. Int Urol Nephrol* 2007; 39: 1227-33.
 29. Stevens LA, Coresh J, Greene T, Levey AS. *Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med* 2006; 354: 2473-83.
 30. Johnson RJ, Segal MS, Srinivas T, Ejaz A, Mu W, Roncal C, Sanchez-Lozada LG, Gersch M, Rodriguez-Iturbe B, Kang DH, Acosta JH. *Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol* 2005; 16: 1909-19.