Family History of Exceptional Longevity Is Associated with Lower Serum Uric Acid Levels in Ashkenazi Jews

Jennifer Yi-Chun Lai, MD, MPH,[*1] *Gil Atzmon, PhD,*[†‡1] *Michal L. Melamed, MD, MHS,*[†] *Thomas H. Hostetter, MD,*[†] *Jill P. Crandall, MD,*[†] *Nir Barzilai, MD,*[†,‡] *and Markus Bitzer, MD*[*†]

OBJECTIVES: To test whether lower serum uric acid (UA) levels are associated with longevity independent of renal function.

DESIGN: Cross-sectional cohort study.

SETTING: Ashkenazi Jewish individuals with exceptional longevity (Longevity Genes Project at Albert Einstein College of Medicine).

PARTICIPANTS: Long-lived individuals (LLI) of Ashkenazi Jewish ethnicity (mean age ± standard deviation 97.7 ± 2.9, n = 365), their offspring (mean age ± standard deviation 68.2 ± 8.2, n = 593) and controls (without family history of longevity, mean age ± standard deviation 72.5 ± 9.9, n = 356).

MEASUREMENTS: Association between UA levels and estimated glomerular filtration rate (eGFR) as well as chronic kidney disease (CKD) stage, and correlation of UA levels of LLI and offspring were determined. Because LLI lack an appropriate control group, UA levels, eGFR, and prevalence of hyperuricemia and CKD stages were compared between offspring and controls.

RESULTS: Offspring were less likely to have hyperuricemia and had lower UA levels than controls. Despite negative correlation between UA levels and eGFR and positive correlation between UA levels and CKD stages, eGFR and the prevalence of CKD stage III to V were not found to be different between offspring and controls. Furthermore, significant association between UA levels in LLI and their offspring (β estimate 0.1544, 95% confidence interval = 0.08 –0.23, $P < .001$) has been observed.

CONCLUSION: Offspring had lower UA levels than controls despite similar renal function, suggesting that other factors such as UA metabolism or renal tubular transport determine UA levels. The association between UA levels and longevity is particularly intriguing because UA levels are potentially modifiable with diet and drugs. **J Am Geriatr Soc 60:745–750, 2012.**

Key words: uric acid; longevity; kidney function

Uric acid (UA) is an organic compound and a potent reducing agent that uricase further oxidizes to allantoin in lower species, but it is the end product of purine catabolism in higher primates and humans.[1] Loss of uricase and associated rise in UA levels are thought to protect against oxidative stress and prolong maximum life span,[2] suggesting a protective role of UA against the aging process; however, in epidemiological studies, high UA levels are a risk factor for cardiovascular disease,[3] stroke,[4] diabetes mellitus (DM),[5] and renal disease.[6] Individuals who achieve exceptional longevity, as well as their offspring, exhibit signs of delayed aging by escaping or delaying age-related chronic diseases,[7] suggesting inheritance of this extreme phenotype.[8] A cohort of Ashkenazi Jews with exceptional longevity (long-lived individuals (LLI)), their offspring, and control subjects, mostly comprising offspring's spouses, chosen to minimize environmental effects, was established in 1998,[9,10] Study of this cohort has identified biomarkers and candidate mechanisms associated with longevity including lipoproteins size[8,10,11] and thyroid hormone levels.[12]

Genetic and environmental factors, including diet, control UA metabolism and excretion.[13] Two-thirds of the daily production of urate is eliminated through urinary excretion, and one-third is excreted through the gastrointestinal tract. Thus, high UA levels and poor renal function are strongly associated.[6,14]

The prevalence of chronic kidney disease (CKD) as defined according to the Kidney Disease Outcomes Quality Initiative (KDOQI), rises continuously with age,[15] with epidemiological studies detecting CKD in 35% to 50% of

From the [*]Division of Nephrology, Department of Internal Medicine, School of Medicine, University of Michigan, Ann Arbor, Michigan; and [†]Departments of Medicine [‡]Genetics, School of Medicine, Albert Einstein College of Medicine, Bronx, New York.

[1]Both authors contributed equally.

Address correspondence to Markus Bitzer, Department of Internal Medicine, University of Michigan, 1150 W. Medical Center Dr, 1570C MSRB2, Ann Arbor, MI, 48105. E-mail: markusbi@umich.edu

DOI: 10.1111/j.1532-5415.2012.03902.x

0002-8614/12/$15.00

individuals aged 70 and older.[16] In addition, individuals with age-associated diseases, including DM and cardiovascular disease, have a high incidence of CKD. Because high UA has been implicated as a risk factor for age-related chronic diseases and subjects with family history of longevity appear to be healthier,[7,8] it was hypothesized that lower UA levels would be associated with longevity because of better renal function.

METHODS

Setting and Participants

Cross-sectional data from three groups were analyzed: Ashkenazi Jewish individuals aged 95 and older and living independently at enrollment in the Einstein Longevity study (LLI) (n = 365; mean age ± SD 98 ± 2.9, 73% female); their offspring (individuals with a family history of longevity, defined as survival of at least one parent to age 95 or older; n = 593; mean age ± SD 68 ± 8.2, 55% female); and age-, sex-, ethnicity-, and sociodemographic-matched controls (individuals without a family history of longevity, defined as both parents having died before age 85; n = 356; mean age ± SD 73 ± 9.9, 57% female). Sixty percent of participants in the control group lived in the same household as their spouse, the offspring (group A). The remainder were individuals living in the same geographic region without any relation to the offspring group (group B). All parameters tested were virtually identical in both control groups (data not shown). Thus, the controls represent control groups A and B combined. Participants were recruited through publicity as described in detail elsewhere.[7,11] Birth certificates or U.S. passports were used to verify age.

Health Outcomes and Definitions

Data used for analysis included medical history, laboratory results, and measurements of body fat. Structured questionnaires were uniformly obtained to identify chronic disease status (including hypertension, DM, myocardial infarction (MI), and stroke) as previously described.[7] Hypertension was defined according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria as blood pressure greater than 130/85 mmHg[17] or self-report of taking antihypertensive medication. All routine blood tests were performed at the Montefiore Medical Center clinical laboratory, which adheres to general laboratory quality guidelines and annually performed quality control checks. Hyperuricemia was defined as UA levels greater than 7 mg/dL in men and greater than 6.5 mg/dL in women. Kidney function was estimated using three creatinine-based formulas: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[18] and the four-variable Modification of Diet in Renal Disease (MDRD) Study[19] for estimated glomerular filtration rate (eGFR) and the Cockcroft-Gault (CG) for estimation of creatinine clearance.[20] Insulin resistance was calculated using the homeostatic model assessment–insulin resistance (HOMA-IR).[21]

Percentage of body fat was assessed using a body fat analyzer (Body Fat Monitor Scale, BF-625; Tanita Corporation of America. Inc., Arlington Heights, IL), and results were used to calculate lean body mass (LBM):

$$\text{LBM} = \text{body weight (kg)} - [\text{body weight (kg)} \times \text{Tanita fat}(\%)]/100$$

Statistical Analysis

Baseline characteristics of offspring and controls were compared. A nonparametric Wilcoxon rank sum test was used to compare age and a two-sample test for proportions was used to compare distribution of sex of offspring and controls. Comparison of age-adjusted chronic disease status (hypertension, DM, MI, and stroke) was performed using logistic regression, and comparison of the other age-adjusted continuous variables, including LBM, weight, UA, albumin, blood urea nitrogen (BUN), creatinine, insulin and HOMA-IR, were completed using linear regression.

Prevalence of hyperuricemia and UA levels were compared between offspring and controls using univariate and multivariate logistic regression and linear regression. UA levels were transformed into natural logarithmic values to achieve a normal distribution. The multivariate regression models were adjusted for age, sex, weight, albumin, BUN, UA, hypertension, CKD, cardiovascular disease, and metabolic syndrome (potential confounders).

The association of UA levels within LLI–offspring pairs was analyzed using a linear mixed random effects model with offspring UA levels as the outcome and LLI UA levels as the explanatory variable. Heritability was calculated as two times the β-estimate (because only one parent was available) of the correlation between UA levels of the offspring and those of their parents (LLI).[22]

Estimated kidney function (CKD-EPI, MDRD, CG) was dichotomized into less than 60 mL/min per 1.73 m^2 (presence of CKD Stages III–V) and 60 mL/min per 1.73 m^2 or greater (absence of CKD Stages III–V) to represent kidney disease status. The association between UA levels and estimated kidney function or kidney disease status was examined in offspring and controls using multivariate linear and logistic regression adjusted for potential confounders and family history of longevity (offspring vs controls). Multivariate linear and logistic regression adjusting for potential confounders was also used to determine whether there was a difference in eGFR and kidney disease status between offspring and controls. eGFR was transformed into natural logarithmic values to achieve normal distribution.

To examine the associations between insulin resistance and the parameters, insulin levels and HOMA-IR, based on serum glucose and insulin levels (as described previously[21]), were used as the response variable in the regression. Multivariate linear and logistic regression were used to examine the association between insulin or HOMA-IR and UA levels, kidney disease status, or family history of longevity (offspring vs controls). HOMA-IR was dichotomized at a cut off of 2.71 in the logistic regression.[23] Insulin and HOMA-IR were transformed into natural logarithmic values to achieve normal distribution.

RESULTS

Subject Characteristics

General characteristics of the participants are presented in Table 1. Despite the matching efforts, offspring and controls (groups A and B combined) differed significantly in age, requiring adjustment for age in any analysis conducted. As expected, the offspring group had fewer MIs ($P = .04$),[8] but no other significant differences were detected between the two groups (Table 1).

Family History of Longevity Is Associated with Lower UA levels

To identify association between UA levels and longevity, the prevalence of hyperuricemia and UA levels of the studied groups were compared. The prevalence of hyperuricemia was 35%, 15%, and 23% in LLI, offspring, and controls, respectively. In univariate and multivariate logistic analysis adjusted for potential confounders, offspring were less likely to have hyperuricemia (Table 2). Furthermore, UA levels were found to be lower in the offspring than in controls according to univariate and multivariate linear analyses (Table 2). UA levels were approximately 1 mg/dL lower in offspring than in controls after back-transformation of natural logarithmic values.

Heritability of UA levels

The observation of lower UA levels in offspring led to the exploration of the association between UA levels in offspring–LLI pairs. A linear mixed random effects model indicated that UA levels in LLI were significantly associated with UA levels in offspring (unadjusted β-estimate = 0.1544, $P < .001$), with a heritability of 0.31. Because there was insufficient clinical information for LLI, the adjusted linear mixed random effects model was not applied.

Association Between UA Levels and Renal Function and Kidney Disease Status

As expected, there was a significant negative correlation between UA levels and eGFR, and higher UA levels were associated with greater likelihood of CKD Stage III to V after adjusting for potential confounders and family history of longevity (offspring vs controls) (Table 3). This association suggests that lower UA levels in offspring are

Table 1. Characteristics of Long-Lived Individuals, Offspring, and Controls

Characteristic	Long-Lived Individuals (n = 365)	Offspring (n = 593)	Controls (n = 356)	Age-Adjusted *P*-Value*
Age, mean ± SD	97.7 ± 2.9	68.2 ± 8.2	72.5 ± 9.9	<.001†
Female, %	73	55	57	.59
Hypertension, %	54	62	67	.44
Diabetes mellitus, %	9	8	10	.29
Myocardial infarction, %	15	4	9	.04
Stroke, %	13	2	3	.73
LBM, kg				
Subjects, n	191	514	247	
Mean ± SD	25 ± 8.4	29 ± 8.0	29 ± 8.1	.93
Weight, kg				
Subjects, n	323	579	273	
Mean ± SD	55 ± 10.6	73 ± 16.1	72 ± 14.2	.25
Serum concentration of uric acid, mg/dL				
Subjects, n	299	518	280	
Mean ± SD	6.2 ± 1.9	5.4 ± 1.5	5.8 ± 1.6	.21
Serum concentration of albumin, g/dL				
Subjects, n	363	591	355	
Mean±SD	3.8 ± 0.4	4.3 ± 0.3	4.3 ± 0.3	.55
Serum concentration of blood urea nitrogen, mg/dL				
Subjects, n	302	524	285	
Mean ± SD	27.3 ± 10.6	20.2 ± 6.1	20.7 ± 6.2	.45
Serum concentration of creatinine, mg/dL				
Subjects, n	300	522	283	
Mean ± SD	1.1 ± 0.4	0.9 ± 0.2	0.9 ± 0.3	.48
Serum concentration of insulin, μU/mL				
Subjects, n	221	353	206	
Mean ± SD	26.5 ± 21.8	23.7 ± 26.4	22.9 ± 22.9	.70
Homeostatic model assessment				
Subjects, n	221	350	206	
Mean ± SD	7.9 ± 8.3	6.4 ± 9.1	6.6 ± 8.8	.94

* Based on comparison between offspring and controls.

† Not adjusted for age.

SD = standard deviation; LBM = lean body mass.

Table 2. Likelihood of Hyperuricemia and Comparison of UA-levels in Offspring and Control in Logistic and Linear Regression (n = 581 vs 280 in Offspring vs Control)

		Hyperuricemia*			UA-levels		
Covariates adjusted	Variable	OR	95% CI	*P*-value	β-estimate	95% CI	*P*-value
Unadjusted	Offspring control	0.58 ref	0.40–0.84	.004	−0.05	(−0.09)–(−0.01)	.009
Age, gender, weight adjusted	Offspring control	0.62 ref	0.40–0.96	.03	−0.05	(−0.09)–(−0.01)	.009
Multivariate adjusted†	Offspring control	0.59 ref	0.35–0.99	.04	−0.06	(−0.1)–(−0.02)	.004

* Hyperuricemia prevalence is 15% vs 23% in offspring vs control; Hyperuricemia is defined as UA-level > 7 mg/dL in male and >6.5 mg/dL in female.
† Adjusted for age, gender, weight, albumin, blood urea nitrogen, hypertension, diabetes mellitus, myocardial infarction, and stroke.
CI = confidence interval; OR = odds ratio; UA = uric acid.

Table 3. Association Between Serum UA-Level and CKD or eGFR in Offspring and Control in Logistic and Linear Regression (n = 565)*

		CKD†			eGFR		
Variable	eGFR formula	OR	95% CI	*P*-value	β-estimate	95% CI	*P*-value
UA-levels	CKD-EPI	1.47	1.21–1.79	<.0001	−0.03	(−0.04)–(−0.02)	<.0001
	MDRD	1.44	1.18–1.76	<.0001	−0.04	(−0.05)–(−0.03)	<.0001
	CG	1.52	1.22–1.89	<.0001	−0.04	(−0.05)–(−0.03)	<.0001

* Adjusted for offspring versus control, age, gender, weight, albumin, blood urea nitrogen, hypertension, diabetes mellitus, myocardial infarction, and stroke.
† CKD is defined as eGFR < 60 mL/min/1.73 m^2 using CKD-EPI formula.
CKD = chronic kidney disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio; UA = uric acid.

due to better renal function because the latter is the main determinant of UA level.

Likelihood of Offspring and Controls Developing Stage III to V CKD

To test this hypothesis, whether offspring have a lower prevalence of kidney disease (Stage III–V CKD) than controls was examined. Based on kidney function estimates, the prevalence of Stage III to V CKD in LLI, offspring, and controls was 76%, 21%, and 29%, respectively, according to the CKD-EPI equation; 52%, 18%, and 23%, respectively, according to the MDRD equation; and 99%, 27%, and 34%, respectively, according to the CG formula. The prevalence of CKD in offspring did not significantly differ from that in controls after adjusting for potential confounders based on the CKD-EPI formula (OR = 0.98, 95% CI = 0.57–1.7; $P = .95$) or the MDRD and CG formulas (data not shown). Furthermore, in multivariate linear analysis with CKD-EPI eGFR as the outcome, family history of longevity was not associated with higher eGFR (offspring vs controls; β-estimate = 0.01; standard error = 0.02; $P = .49$, same results were obtained using MDRD and CG, data not shown). The formula generated vastly different eGFR values in participants aged 90 and older.

In summary, family history of longevity is not associated with better kidney function. These findings suggest that, despite the reported association between high UA levels and poor kidney function, and similar kidney function in offspring and controls, offspring have lower UA levels independent of kidney function.

Insulin Resistance and LBM Analyses

No significant differences between offspring and controls were detected for insulin levels and insulin resistance assessed using continuous and dichotomized HOMA-IR.[23] In addition, no associations between HOMA-IR or insulin levels and Stage III to V CKD or UA levels were found (data not shown). Muscle mass has been shown to influence serum creatinine levels.[24] Nevertheless, replacing weight with LBM for covariate adjustment did not influence the significance of the statistical comparison of presence of CKD Stage III to V or distribution of eGFR between offspring and controls.

DISCUSSION

Many factors contribute to the increasing number of LLI worldwide. A limitation of studying factors that distinguish exceptionally LLI is the lack of an appropriate control group. This limitation was overcome by comparing offspring with appropriate controls. This well-defined group of genetically relatively homogeneous subjects of Ashkenazi descent LLI, offspring, and controls allowed detection of differences that may require a much larger number of participants when studying heterogeneous populations. Examination of this cohort has revealed lower prevalence of age-associated diseases and better cardiovascular, cognitive, and metabolic performance than in age- and ethnicity-matched subjects without a family history of longevity.[7] Thus, it was hypothesized that lower UA levels would be associated with longevity because of relatively better renal function.

UA and Longevity

It has been proposed that higher UA levels across species are an evolutionary survival advantage of long-lived species based on the free radical theory of aging, which postulates that opposing free radicals such as reactive oxygen species damaging components of the cellular machinery through a natural defense system of anti-oxidants such as UA leads to longer life period.[1,2] By contrast, in humans, higher UA levels have been associated with greater morbidity and mortality. To contribute to the understanding of UA in human longevity, it was determined that the prevalence of hyperuricemia is lower in offspring of LLI than in controls. Moreover, offspring of LLI are less likely to have hyperuricemia and have UA levels that are close to 1 mg/dL lower than controls. Even though these findings do not uncover a mechanistic link, it could be hypothesized that further elevation of UA levels negatively affects longevity, possibly through vascular endothelial injury.[25] The moderate calculated heritability of UA levels in LLI–offspring pairs detected suggests that genetic components contribute to the determination of UA levels. Overall, our findings support the hypothesis that lower UA levels are associated with longevity. Future studies may explore UA as a biomarker for longevity and as a modifiable risk factor for premature mortality.

Kidney Function and Longevity

Renal function is the major determinant of UA levels, because glomerular filtration is the main mode of elimination of UA. GFR represents renal function and is commonly assessed by measuring serum creatinine concentration and calculating eGFR. Unfortunately, eGFR values calculated using various formulas differ significantly, particularly in older adults,[26] so three independently developed formulas were used. The CG formula, which estimates creatinine clearance, probably underestimates GFR, whereas the MDRD formula may overestimate the true value in older adults.[27] It has been proposed that the CKD-EPI formula is more accurate according to data from different studies including the National Health and Nutrition Examination Survey, but the number of older study participants is limited.[18]

Because none of the equations have been validated in LLI and generate vastly different eGFR values in subjects aged 90 and older, the analysis was focused on offspring and controls. Furthermore, participants were classified according to kidney disease status (Stages III–V) using an eGFR of 60 mL/min per 1.73 m^2 as a cut off, according to the KDOQI guideline to determine presence (eGFR $<$ 60 mL/min per 1.73 m^2) or absence (eGFR $\geq$ 60 mL/min per 1.73 m^2) of Stage III to V CKD. In addition, adjusted multivariate analysis replacing weight with LBM failed to detect an association between continuous eGFR or kidney disease status and offspring status, but only a subgroup of subjects had data on LBM available. In summary, the findings indicate that a family history of longevity is not linked to better renal function in Ashkenazi Jews.

This observation is somewhat surprising because it has been reported that individuals with a family history of longevity in this cohort delay or escape other chronic diseases,[8] and poor renal function has been found to be associated with greater morbidity and mortality in other cohorts.[28] Nevertheless, it is possible that using serum creatinine values to calculate eGFR does not accurately reflect true renal function in older adults.[18–20] Other methods to estimate kidney function, including serum cystatin C measurements, should be evaluated in this age group.[29] The finding of lower UA levels without difference in kidney function in offspring as determined using three different formulas suggests that factors independent of GFR, possibly diet and genetic components of UA metabolism, influence UA levels.

Kidney Function and UA

Epidemiological evidence supports that higher UA levels are associated with poorer renal function.[6,14] Examining all participants, UA levels exhibiting a negative association with eGFR and a positive association with kidney disease status were found. In addition, lower eGFR and higher UA levels were found in LLI than in offspring or controls, consistent with age-associated decline in renal function and increase in UA levels and with previously reported negative correlation between UA levels and eGFR.[6,14]

Insulin Resistance and UA

Insulin resistance is the basis for metabolic syndrome and DM, which are accelerated with aging. Higher UA levels are associated with greater insulin resistance, possibly through inhibition of nitric oxide bioavailability, which is known to promote glucose uptake by insulin.[30] No significant associations with the tested parameters were detected. This may be because the HOMA-IR model, which does not account for endogenous beta-cell function, was used.

CONCLUSION

Heritable lower UA levels have been observed in genetically relatively homogeneous individuals with a family history of longevity. Even though the participants studied were not representative of the general population, the findings support the hypothesis that lower UA levels may constitute a marker for longevity in humans. It remains to be determined whether lower UA levels are a cause or an effect of the delay or escape of chronic diseases and whether UA has other properties in addition to oxidant scavenger. Nevertheless, these findings are intriguing because UA levels are modifiable using diet or drugs that lower UA levels. Several interventional studies are underway to attempt to reveal mechanistic links between UA and chronic diseases (http://clinicaltrials.gov/).

ACKNOWLEDGMENT

We thank Dr. Jocelyn Wiggins for critical review of the manuscript.

Conflict of Interest: The authors have no financial or any other kind of personal conflicts with this paper. Thomas Hostetter: consultant for Eli Lilly, Bristol-Myers Squibb, Genzyme (no direct conflict with presented study).

Author Contributions: Nir Barzilai and Markus Bitzer: study concept and design. Jennifer Yi-Chun Lai and Gil Atzmon: data collection and statistical analysis. Jennifer Yi-Chun Lai, Gil Atzmon, Michal Melamed, Thomas Hostetter, Nir Barzilai, Markus Bitzer: interpretation of data and discussion of findings. Jennifer Yi-Chun Lai, Gil Atzmon, and Markus Bitzer: preparation of manuscript.

Sponsor's Role: None.

Funding: Markus Bitzer was supported by the National Kidney Foundation. Michal Melamed is supported by K23 DK078774 from the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health.

REFERENCES

1. Oda M, Satta Y, Takenaka O et al. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol 2002;19:640–653.
2. Cutler RG. Urate and ascorbate: their possible roles as antioxidants in determining longevity of mammalian species. Arch Gerontol Geriatr 1984;3:321–348.
3. 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;283:2404–2410.
4. Kim SY, Guevara JP, Kim KM et al. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Rheum 2009;61:885–892.
5. Dehghan A, van Hoek M, Sijbrands EJ et al. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 2008;31:361–362.
6. Obermayr RP, Temml C, Gutjahr G et al. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407–2413.
7. Atzmon G, Schechter C, Greiner W et al. Clinical phenotype of families with longevity. J Am Geriatr Soc 2004;52:274–277.
8. Atzmon G, Rincon M, Rabizadeh P et al. Biological evidence for inheritance of exceptional longevity. Mech Ageing Dev 2005;126:341–345.
9. Barzilai N, Rossetti L, Lipton RB. Einstein's Institute for Aging Research: collaborative and programmatic approaches in the search for successful aging. Exp Gerontol 2004;39:151–157.
10. Barzilai N, Gabriely I, Gabriely M et al. Offspring of centenarians have a favorable lipid profile. J Am Geriatr Soc 2001;49:76–79.
11. Barzilai N, Atzmon G, Schechter C et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA 2003;290: 2030–2040.
12. Atzmon G, Barzilai N, Hollowell JG et al. Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 2009;94:1251–1254.
13. Gulbrandsen CL, Morton NE, Rao DC et al. Determinants of plasma uric acid. Hum Genet 1979;50:307–312.
14. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleve Clin J Med 2008;75(Suppl 5):S13–S16.
15. U.S. Renal Data System. 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010.
16. Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–2047.
17. Chobanian AV, Bakris GL, Black HR et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252.
18. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
19. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
21. Matthews DR, Hosker JP, Rudenski AS et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
22. Ward PJ. Parent-offspring regression and extreme environments. Heredity 1994;72:574–581.
23. Geloneze B, Repetto EM, Geloneze SR et al. The threshold value for insulin resistance (HOMA-IR) in an admixtured population IR in the Brazilian Metabolic Syndrome Study. Diabetes Res Clin Pract 2006;72:219–220.
24. Baxmann AC, Ahmed MS, Marques NC et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol 2008;3:348–354.
25. Kim SY, Guevara JP, Kim KM et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010;62:170–180.
26. Botev R, Mallie JP, Couchoud C et al. Estimating glomerular filtration rate: Cockcroft-Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. Clin J Am Soc Nephrol 2009;4:899–906.
27. Fliser D. Assessment of renal function in elderly patients. Curr Opin Nephrol Hypertens 2008;17:604–608.
28. Fried LF, Shlipak MG, Crump C et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. J Am Coll Cardiol 2003;41:1364–1372.
29. Fried LF. Creatinine and cystatin C: What are the values? Kidney Int 2009;75:578–580.
30. Borges RL, Ribeiro AB, Zanella MT et al. Uric acid as a factor in the metabolic syndrome. Curr Hypertens Rep 2010;12:113–119.