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

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Abstract

Objectives—While long-lived species exhibit higher serum uric acid (UA) levels than short-lived species, higher UA-levels have been linked to diseases associated with premature death in humans. We tested whether lower UA-levels are associated with longevity independent of renal function as secretion in the urine is the major mode of elimination of UA.

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 (±SD) 98(±2.9) years, n=365), their offspring (mean age 68(±8.2), n=593) and controls (without family history of longevity, mean age 73(±9.9), n=356).

Measurements—Association of UA-levels with estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD)-stages as well as correlation of UA-levels between LLI and offspring were determined. As 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 exhibit hyperuricemia and had lower UA-levels compared to controls. Despite negative correlation of UA-levels with eGFR and positive correlation with increasing CKD-stage, eGFR and prevalence of CKD-stages were not found to be different between offspring and controls. Furthermore, significant association of UA-level between LLI and their offspring (β-estimate: 0.1544, 95% CI: 0.08–0.23, P-value: 0.0003) has been observed.

Conclusion—Offspring exhibit lower UA-levels compared to controls despite similar renal function suggesting that other factors like UA metabolism or renal tubular transport determining

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UA-levels. The association of UA-levels with longevity is particularly intriguing as UA-levels are potentially modifiable by diet and drugs.

Keywords

uric acid; longevity; kidney function

INTRODUCTION

Uric acid (UA) is an organic compound and a potent reducing agent that is further oxidized to allantoin by uricase in lower species, but 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, elevated UA-levels are a risk factor for cardiovascular disease[3], stroke[4], diabetes mellitus (DM)[5], and renal disease[6]. Subjects 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 composed of 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].

UA metabolism and excretion is controlled by genetic and environmental factors, including diet[13]. Two thirds of the daily production of urate is eliminated by urinary excretion and one third is excreted via the GI tract. Thus, high UA-levels and decreased renal function are strongly associated[6, 14].

The prevalence of CKD as defined by KDOQI (Kidney Disease Outcomes Quality Initiative) rises continuously with age (USRDS 2010) with epidemiologic studies detecting CKD in 35–50% of subjects over age 70[15]. In addition, patients who suffer from age-associated diseases including DM and cardiovascular disease have a high incidence of CKD[16]. 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], we hypothesize that lower UA-levels are associated with longevity due to relative better renal function.

METHODS

Setting and Participants

Cross-sectional data from three groups were analyzed: 1) Ashkenazi Jewish subjects of the Einstein Longevity study, living independently at age 95 years or older at enrollment (LLI) (n=365; Mean-age ± SD: 98±2.9, 73% female), 2) their offspring (subjects with 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 3) age-, gender-, ethnicity-, and socio-demographic-matched controls (subjects without family history of longevity defined as both parents deceased before age 95; n=356; mean-age ± SD: 73±9.9, 57% female). Sixty percent of the subjects in the control group lived in the same household as their spouse, the offspring (group A). The remainder was subjects living in the same geographic region without any relation to the offspring group (group B). However, all parameters tested were virtually identical in both control groups (data not shown). Thus, the controls represent control groups A and B combined. Subjects 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 (HTN), DM, myocardial infarction (MI), and stroke) as described[7]. Hypertension was defined by JNC7 criteria as blood pressure >130/85 mmHg[17] or self-reported being on anti-hypertensive medication. All routine blood tests were performed by 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 >7 mg/dl in males and >6.5 mg/dl in females. Kidney function was estimated using three creatinine based formulas: CKD-EPI[18] and 4-variable Modification Diet in Renal Disease (MDRD) Study[19] for eGFR and 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 by Tanita BIA 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):

$$\mathrm{LBW}=\mathrm{Body\ weight(kg)}-[\mathrm{Bodyweight(kg)}^{*}\mathrm{Tanita\ Fat(\%)}]/100$$

Statistical Analysis

Baseline characteristics were compared between offspring and controls. Non-parametric Wilcoxon rank sum test was applied to compare age, and Two-Sample Test for Proportions was used to compare distribution of sex. Comparison of age-adjusted chronic disease status (HTN, DM, MI, and stroke) were performed using logistic regression, and comparison of the other age-adjusted continuous variables, including LBM, weight, UA, albumin, 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 as well as 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, HTN, CKD, cardiovascular disease and metabolic syndrome (potential confounders).

The association of UA-levels within LLI-offspring pairs was analyzed by linear mixed random effects model with offspring UA-levels as the outcome and LLIUA-levels as the explanatory variable. Heritability was calculated as 2-times the β-estimate (as only one parent was available) of the correlation between the UA-levels of the offspring over the parents (LLI)[22].

Estimated kidney function (CKD-EPI, MDRD, CG) was dichotomized into <60ml/min/1.73m^2 (presence of CKD-stages III–V) and ≧60ml/min/1.73m^2 (absence of CKD-stages III–V) to represent kidney disease status. We examined the association of UA-levels with estimated kidney function or kidney disease status in offspring and controls by multivariate linear and logistic regression adjusted for potential confounders as well as family history of longevity (offspring versus controls). Multivariate linear and logistic regression adjusting for potential confounders were also applied to determine whether there is 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 of insulin resistance with our parameters, we used insulin levels and HOMA-IR, based on serum glucose and insulin levels (as described[21]), as the response

variable in the regression. We applied multivariate linear and logistic regression to examine the association between insulin/HOMA-IR and UA-levels, kidney disease status, offspring and 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, off spring and controls (both groups A and B combined) differ significantly in age, requiring adjustment for age in any analysis conducted. As expected, the offspring group had fewer MIs (P=0.04)[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 of UA-levels with longevity we compared prevalence of hyperuricemia and UA-levels between the studied groups. The prevalence of hyperuricemia was 35%, 15%, and 23% in LLI, offspring and controls, respectively. In both univariate and multivariate logistic analysis adjusted for potential confounders, offspring were less likely to have hyperuricemia (Table 2). Furthermore, we found UA-levels to be lower in the offspring compared to the controls using 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 us to explore the association of UA-levels between offspring-LLI pairs. Using linear mixed random effects model, it indicated that UA-levels of LLI were significantly associated with offspring UA-levels (unadjusted β-estimate = 0.1544, P-value < 0.001), providing a heritability of 0.31. Due to insufficient clinical information of LLI the adjusted linear mixed random effects model was not applied.

Association of UA-levels with Renal Function and Kidney Disease Status

As expected, UA-levels exhibited a significant negative correlation with eGFR, and higher UA were associated with increased likelihood for kidney disease status (CKD-stage III–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 due to better renal function as latter is the main determinant of UA-levels.

Likelihood to Develop CKD-Stage III–V among Offspring and Controls

To test this hypothesis, we examined whether offspring have a lower prevalence of kidney disease (CKD-stage III–V) compared to controls. Based on kidney function estimates, the prevalence of CKD-stage III–V in LLI, offspring and controls was 76%, 21%, and 29% (CKD-EPI-equation); 52%, 18%, and 23% (MDRD-equation); 99%, 27%, and 34% (CG), respectively. The prevalence of CKD in offspring did not significantly differ from the controls after adjusting for potential confounders based on CKD-EPI formula (offspring vs. controls OR=0.98; 95% CI=0.57–1.7; P-value=0.9464) as well as MDRD and CG formula (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; SE=0.02; P-value=0.4939, same results were obtained using MDRD and CG: data not shown). Of note, the formula generated vastly different eGFR

values among subjects age 90 years and older. In summary, family history of longevity is not associated with better kidney function. These findings suggest that despite the reported association of higher UA-levels with reduced kidney function, independency of family history of longevity and similar kidney function among 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 by continuous and dichotomized HOMA-IR[23]. In addition, no associations of HOMA-IR or insulin levels with CKD-stage III–V status 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 comparison of CKD-stage III–V status or 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. We circumvented this limitation by comparing offspring with appropriate controls. This well-defined group of genetically relatively homogeneous subjects of Ashkenazi descendent LLI, offspring and controls allows detection of differences that may require much larger number of subjects when studying heterogeneous populations. Examination of this cohort has revealed decreased prevalence of age-associated diseases and better cardiovascular, cognitive and metabolic performance compared to age- and ethnicity-matched subjects without family history of longevity[7]. Thus, we hypothesized that lower UA-levels are associated with longevity due to relative better renal function.

UA and Longevity

Higher UA-levels across species have been proposed as an evolutionary survival-advantage of long-lived species based on the free-radical theory of aging that postulates opposing free radicals like reactive oxygen species (ROS) damaging components of the cellular machinery by a natural defense system of anti-oxidants like UA leads to longer live[1–2]. In contrast, within the human population higher UA-levels have been associated with increased morbidity and mortality. To contribute to the understanding of UA in human longevity, we determined that the prevalence of hyperuricemia is lower in offspring compared to controls. Moreover, offspring are less likely to have hyperuricemia, and have close to 1 mg/dl lower UA-levels than control subjects. Even though these findings do not allow a mechanistic link, it could be hypothesized that further elevation of UA-levels negatively affect longevity possibly through vascular endothelial injury[25]. The detected moderate calculated heritability of UA-levels in LLI-offspring pairs suggests genetic components contributing 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 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, as 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 by various formulas differ significantly particularly among older adults[26]. Therefore, we used three independently developed formulas. The CG formula, which estimates the creatinine clearance, likely underestimates GFR whereas the MDRD Study

formula may overestimate the true value in older adults[27]. The CKD-EPI formula has been proposed to perform more accurately using data from different studies including NHANES (National Health and Nutrition Examination Survey), but the number of older study subjects is limited[18].

As none of the equations have been validated in LLI and generate vastly different eGFR values in subjects over age 90, we focused our analysis on offspring and control groups. Furthermore, we classified subjects into kidney disease status (CKD-stage III–V) using an eGFR of 60 ml/min/1.73m^2 as a cut off according to the KDOQI guideline to determine presence (eGFR <60 ml/min/1.73m^2) or absence (eGFR ≥60ml/min/1.73m^2) of CKD-stage III–V. 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, our findings implicate that a family history of longevity is not linked with better renal function in Ashkenazi Jews. This observation is somewhat surprising as it has been reported that subjects with family history of longevity in this cohort delay or escape other chronic diseases[8] and decreased renal function is associated with increased morbidity and mortality in other cohorts[28]. However, 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]. Nevertheless, our finding of lower UA-levels without difference in kidney function in offspring as determined by three different formulas suggests that UA-levels are influenced by factors independent of GFR, possibly diet and genetic components of UA metabolism.

Kidney Function and UA

Epidemiologic evidence supports that higher UA-levels are associated with decreased renal function[6, 14]. Examining all subjects we found UA-levels exhibiting a negative association with eGFR and a positive association with kidney disease status. In addition, lower eGFR and higher UA-levels were found among LLI compared to 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

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

CONCLUSION

Heritable lower UA-levels have been observed in genetically relative homogenous subjects with family history of longevity. Even though the subjects studied are 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 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 as UA-levels are modifiable by diet or drugs that lower UA-levels. Several interventional studies are underway attempting to reveal mechanistic links between UA and chronic diseases (http://clinicaltrials.gov/).

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Table 1

Characteristics of long-lived subjects, offspring, and controls

	Long-lived subjects	Offspring	Controls	Age-adjusted P-value*
No. of subjects	365	593	356	
Age, Mean (± SD)	98 (± 2.9)	68 (± 8.2)	73 (± 9.9)	<0.00001[a]
% female	73%	55%	57%	0.59
% with HTN	54%	62%	67%	0.44
% with DM	9%	8%	10%	0.29
% with MI	15%	4%	9%	0.04
% with stroke	13%	2%	3%	0.73
LBM (kg)				
No. of subjects	191	514	247	
Mean (± SD)	25 (± 8.4)	29 (± 8.0)	29 (± 8.1)	0.93
Weight (kg)				
No. of subjects	323	579	273	
Mean (± SD)	55 (± 10.6)	73 (± 16.1)	72 (± 14.2)	0.25
UA (mg/dl)				
No. of subjects	299	518	280	
Mean (± SD)	6.2 (± 1.9)	5.4 (± 1.5)	5.8 (± 1.6)	0.21
Albumin (g/dl)				
No. of subjects	363	591	355	
Mean (± SD)	3.8 (± 0.4)	4.3 (± 0.3)	4.3 (± 0.3)	0.55
BUN (mg/dl)				
No. of subjects	302	524	285	
Mean (± SD)	27.3 (± 10.6)	20.2 (± 6.1)	20.7 (± 6.2)	0.45
Creatinine (mg/dl)				
No. of subjects	300	522	283	
Mean (± SD)	1.1 (± 0.4)	0.9 (± 0.2)	0.9 (± 0.3)	0.48
Insulin (μU/ml)				
No. of subjects	221	353	206	
Mean (± SD)	26.5 (± 21.8)	23.7 (± 26.4)	22.9 (± 22.9)	0.70
HOMA				
No. of subjects	221	350	206	
Mean (± SD)	7.9 (± 8.3)	6.4 (± 9.1)	6.6 (± 8.8)	0.94

*P-value is based on the comparison between offspring and control

[a]not adjusted for age

SD: standard deviation, HTN: hypertension, DM: diabetes mellitus, MI: myocardial infarction, LBM: lean body mass; HOMA: homeostatic model assessment; Serum concentrations of: UA (uric acid), BUN (blood urea nitrogen), Albumin, creatinine, Insulin

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)

Covariates adjusted	Variable	Hyperuricemia*			UA-levels		
		OR	95% CI	P-value	β-estimate	95% CI	P-value
Unadjusted	Offspring	0.58	0.40–0.84	0.004	−0.05	(−0.09)–(−0.01)	0.009
	Control	1					
Age, gender, weight adjusted	Offspring	0.62	0.40–0.96	0.03	−0.05	(−0.09)–(−0.01)	0.009
	Control	1					
Multivariate adjusted†	Offspring	0.59	0.35–0.99	0.04	−0.06	(−0.1)–(−0.02)	0.004
	Control	1					

*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

UA: uric acid; CI: confidence interval; OR: odds ratio.

Table 3

Association between serum UA-level and CKD or eGFR in offspring and control in logistic and linear regression (n=565)[†]

Variable	eGFR formula	CKD[*]			eGFR		
		OR	95% CI	P-value	β-estimate	95% CI	P-value
UA-levels	CKD-EPI	1.47	1.21–1.79	<0.0001	−0.03	(−0.04)–(−0.02)	<0.0001
	MDRD	1.44	1.18–1.76	<0.0001	−0.04	(−0.05)–(−0.03)	<0.0001
	CG	1.52	1.22–1.89	<0.0001	−0.04	(−0.05)–(−0.03)	<0.0001

[†]adjusted for offspring versus control, age, gender, weight, albumin, blood urea nitrogen, hypertension, diabetes mellitus, myocardial infarction, and stroke.

CKD: chronic kidney disease,

[*]CKD is defined as eGFR <60 ml/min/1.73 m^2 using CKD-EPI formula

UA: uric acid; CI: confidence interval; eGFR: estimated glomerular filtration rate; OR: odds ratio;