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Uric Acid, Hypertension, and CKD among Alaska Eskimos—the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) Study

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Abstract

It is unknown what role uric acid may play in the increasing cardiovascular disease (CVD) among Alaska Eskimos. Uric acid is associated with both hypertension (HTN) and chronic kidney disease (CKD). We analyzed 1078 Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) participants. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measures using the MDRD equation. CKD was defined by an eGFR of <60ml/min/1.73m^2. We adjusted for age, sex, education, diabetes, hypertension (or eGFR), obesity, lipids, and smoking status; 7% (n=75) had prevalent CKD. eGFR decreased with increasing tertiles of serum uric acid. ($p<0.001$) Uric acid was independently associated with prevalent CKD (Adjusted Odds Ratio [OR] and 95% confidence interval [CI] of 2.04 (1.62–2.56), respectively). 21% (n=230) had prevalent HTN; Uric acid was independently associated with prevalent HTN (Adjusted OR 1.2, 95% CI 1.1–1.5). Uric acid is independently associated with prevalent CKD and HTN in this population.

Keywords

Alaska Eskimos; chronic kidney disease; epidemiology; hypertension; uric acid

Introduction

Uric acid levels have been shown to be independently associated with hypertension (HTN)[1–3], prehypertension [4], cardiovascular disease (CVD) [5–7], and mortality.[8–10] Additionally, elevated uric acid has been found to be independently associated with both

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Conflict of Interest

None of the above authors listed have any financial conflict of interests to disclose.

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prevalent [11, 12] and incident chronic kidney disease (CKD)[11, 13, 14], as well as with risk of myocardial infarction, stroke, and all-cause mortality among those with CKD.[15]

Since patients with hyperuricemia often have an excess of comorbid CVD risk factors, there has been controversy as to whether these associations actually reflect a role for elevated uric acid in causal pathophysiological process leading to HTN, CKD, or cardiovascular morbidity and mortality.[16] Importantly, laboratory animal experiments following uricase inhibition and *in vitro* experimental models support a mechanistic link between hyperuricemia and manifestations of both cardiovascular and kidney disease. These include uric acid induced glomerular HTN and cortical vasoconstriction,[17, 18] endothelial dysfunction,[19] renal hypertrophy,[20] glomerulosclerosis, and interstitial fibrosis[21] as well as stimulation of inflammatory signaling in vascular cells.[22, 23]

Alaska Eskimos represent a unique population that has undergone recent drastic changes in diet and lifestyle. Participants in the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study exhibit an excess of CVD.[24] We used GOCADAN data to determine associations of serum uric acid with CKD and with HTN at the baseline exam in this population.

Subjects and Methods

Study Population

GOCADAN is a population-based study to investigate the genetic and non-genetic determinants of CVD and its risk factors in Alaska Natives. Details of the study design and methods are available elsewhere.[25] Briefly, a total of 1214 predominantly Inupiat Eskimo participants were recruited from October 2000 through April 2004 in the Norton Sound region of Alaska. GOCADAN was approved by the Research and Ethics Review Board of Norton Sound Health Corporation who request that we use the term Alaska Eskimos. Additionally, the study was approved by all relevant Institutional Review Boards. Participants were members of extended families but the cohort represented 75% of all age-eligible residents of the villages. Participants completed an interviewer-administered survey of demographics and medical history, and underwent a complete physical examination, which included the collection of blood, urine, and anthropometric measurements.

Outcomes

CKD—Our primary outcome for this analysis was prevalent CKD, which was defined as an estimated glomerular filtration rate (eGFR) of <60ml/min/1.73m^2.[26] We calculated eGFR for participants from a measured serum creatinine value using the MDRD equation[27] Creatinine assays were performed on stored serum specimens in 2009 using an enzymatic assay on the Vitros 5,1 platform with an interassay CV of 1.8% (Ortho Clinical Diagnostics, Rochester, NY).

Hypertension (HTN)—Our secondary outcome was prevalent HTN. Right brachial blood pressure (BP) was measured three times following a 5-minute rest with a mercury sphygmomanometer (W. A. Baum Co., Inc., Copiague, NY). The mean of the second and third measurements was used for the analyses. Participants were categorized as having prevalent HTN if they had a systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or were taking antihypertensive medication at the time of the exam without an alternative indication for its use documented in the medical record.[28]

Uric acid—Our primary predictor was serum uric acid. Serum uric acid was determined along with creatinine using an uricase method in dry slide format on the Vitros 5,1 platform with an interassay CV of 1.5%. (Ortho Clinical Diagnostics, Rochester, NY).

Covariates

Sociodemographics—Age was based on verified date of birth and years of education were by self-report.

Clinical parameters—Body Mass Index (BMI) was calculated from the measured weight and height according to a standard formula and metric conversion [BMI=weight (lb)/ height^2 (in) * 704.5 kg in^2/lb m$^{2)}$]. Obesity was defined as a BMI ≥ 30 kg/m^2. Diabetes was defined in GOCADAN by participants' report of previous or current use of either insulin or oral hypoglycemic medication; a fasting plasma glucose ≥ 126 mg/dL or 2-hour plasma glucose ≥ 200 mg/dL after ingesting a 75g oral glucose load, both at the baseline exam.[29] Albuminuria is defined as a urine albumin to creatinine ratio ≥ 30mg/g. Urine albumin and creatinine were measured from a single morning sample. Urine albumin was assayed using an immunoturbidometric method (Diasorin SPQ reagents and calibrators, Stillwater, MN) on the Roche-Hitachi 717 platform (Basel, Switzerland) with the lowest assayed standard at 5.7mg/L and a coefficient variation of 1.6% at 44 mg/L. Urine creatinine was assayed using Vitros 250 CREA slides (Ortho Clinical Diagnostics, Raritan, NJ) and a 2-point system, with a coefficient variation of 1.8% at 1.47g/L. Smoking status was self-reported during the structured interview portion of the examination and was categorized as former, current, or never smoker.

Additional Laboratory Values—Fasting serum lipids were measured on the Roche-Hitachi 717 platform and high sensitivity C-reactive protein (hsCRP) on the Vitros 950 platform as reported previously.[25]

Statistical Analysis

From the original GOCADAN cohort (n=1214) we excluded participants without laboratory data (n = 135) or with age <18 years (n = 1), leaving a study sample of 1078 participants, or 89% of the baseline cohort. For the HTN specific analyses an additional n=1 was dropped due to lack of data leaving a study sample of 1077.

Descriptive statistics were calculated using means and standard deviations for continuous variables and frequencies (proportions) for categorical variables. The differences between participants with and without CKD were compared by t-test or Chi-square test as appropriate. Triglycerides and hsCRP required log-transformation because of skewed distributions and thus a two-sample comparison test was conducted for these variables. We present the geometric mean and 95% confidence intervals (CI). For serum uric acid level tertiles, p-values were calculated using a nonparametric trend test, which is an extension of the Wilcoxon rank-sum test, for trend across uric acid level tertiles.

The association of prevalent CKD with uric acid was assessed by logistic regression models using uric acid as a continuous variable and eGFR as either a dichotomized or continuous variable. We first examined the univariate, or unadjusted, association of uric acid and CKD and derived odds ratios (OR) and 95% CIs. We then conducted a stepwise multivariate analysis, successively adjusting for covariates, including systolic BP, that were selected *a priori*, as potentially influencing the association of uric acid with prevalent CKD. We derived the corresponding adjusted ORs and 95% CIs for each of the models.

We computed the proportion of participants with prevalent HTN. Differences between participants with and without HTN were compared by t-test or Chi-square test as appropriate. Triglycerides and hsCRP were log-transformed, as noted above.

To assess the association between prevalent HTN with uric acid as a continuous variable, we performed a series of logistic regressions. As before, first examining univariate associations then proceeding to the same stepwise multivariate analysis approach described previously, now adjusting for eGFR rather than systolic BP in model 4. We derived the corresponding adjusted ORs and 95% CIs for each of the models.

Additionally, we repeated the analyses using a method to account for our population structure of large and inter-related families.[30] Our results did not change with adjustment of relatedness and so we present the original logistic regression models.

We further adjusted the logistic and linear regression models for uric acid and risk of prevalent CKD for diuretic use, using detailed medication data from the structured medical history interview; only about 10% of participants reported taking any diuretic drug. A sensitivity analysis showed that there was almost no effect of diuretics on any of our CKD models, so our original models are presented to maximize precision. The sensitivity analysis for prevalent HTN revealed that the first 3 models remained statistically significant whether or not patients receiving diuretics were included or excluded from analysis. However, the subsequent models, numbers 4 and 5, were no longer statistically significant, perhaps due to reduced sample size or over saturation of the model. The original models are presented.

STATA version 11.0 (StataCorp LP, College Station, TX) and SAS version 9.1 (SAS Institute Inc., Cary, NC) was used for all data manipulation and analysis.

Results

Of the 1078 GOCADAN participants, 7% (n=75) had prevalent CKD as defined by an eGFR <60ml/min/1.73m^2 using the MDRD equation. Participants with CKD were more likely to be older, have diabetes, or have HTN compared to participants without CKD. (Table 1)

With increasing tertiles of serum uric acid, GOCADAN participants had higher systolic BP, BMI, and triglyceride levels. (Table 2) There was a significant trend of progressively lower eGFR associated with increasing tertiles of serum uric acid. (Table 2) After adjustment for covariates, uric acid was independently associated with prevalent CKD (Adjust Odds Ratio 2.04, 95% confidence interval [1.62–2.56]. (Table 3)

Nearly a quarter, or 21% (n=230) of the participants had prevalent HTN. Those with HTN were more likely to be older, diabetic, or albuminuric compared to those without HTN. (Table 4) Uric acid was independently associated with prevalent HTN (Adjust Odds Ratio 1.24, 95% confidence interval [1.06–1.46]. (Table 5)

Discussion

In this unique population with higher rates of CVD but lower rates of diabetes, hyperlipidemia, and CKD than the general U.S. population, serum uric acid concentration was independently associated with both prevalent CKD and HTN. These results add to those from other observational studies in populations with differing patterns of comorbidities and risk factors in suggesting a role for uric acid in renal and cardiovascular disorders.

We have previously shown that prevalence of CKD Stages 1 and 2, as defined by albuminuria, is lower in Alaska Eskimos[24] than reported for the U.S. general population.[31]

In this study we also found that fewer than 10% of GOCADAN participants had prevalent CKD stages 3–5, as defined by reduced eGFR, again lower than in the U.S. general population. As reported previously for albuminuria (30), those with CKD as defined by reduced eGFR were more likely to be older, have diabetes, or have HTN compared to those without CKD. The reasons for this lower rate of CKD are not clear but in part may be due to the low rates of diabetes.

Elevated uric acid has been shown to increase the risk for both prevalent and incident CKD in other populations and to be associated with albuminuria in otherwise-healthy pre-hypertensive individuals[12, 32–35] Uric acid was a significant predictor of incident CKD in a Chinese population.[36] and has been independently associated with progression of kidney disease in some, but not all studies[37], and even in otherwise healthy individuals without hypertension.[12, 38] Indeed, in one small randomized trial, pharmacologic lowering of serum uric acid with allopurinol decreased CKD progression significantly at one year[39] and a recent secondary analysis suggests that uric acid lowering contributes to nephroprotection by losartan in the setting of diabetic nephropathy.[40]

A quarter of the GOCADAN participants had prevalent HTN. Compared to those without HTN, participants with HTN were more likely to be older, diabetic, or albuminuric. Uric acid was independently associated with prevalent HTN even after adjustment for sociodemographics, clinical parameters, and laboratory values, including eGFR. The findings are consistent with other studies that found an almost doubled risk for hypertension among those with elevated uric acid in a screened adult Japanese cohort[2], male workers in southern Italy[1], and Framingham Study participants.[3]As in the case of CKD progression, the recent observation that uric acid lowering with allopurinol lowers BP in pediatric patients with recent-onset essential hypertension suggests the possibility that the association of hyperuricemia with hypertension may be of pathophysiologic importance.[41]

Serum uric acid levels in humans are primarily determined by renal uric acid clearance, with 90% of clinically-recognized hyperuricemia resulting from its impaired renal excretion.[42] Recent genome-wide association studies (GWAS) in European Caucasian populations have shown consistently that variants in the solute carrier protein 2 family member 9 (*SLC2A9*) gene are associated with serum uric acid levels [43–45]. Similarly, we have reported the significant heritability of serum uric acid levels in Mexican-Americans[46], American Indians in the Strong Heart Family Study[47] and in Zuni Indians[48], albeit with differing apparent candidate gene associations. We have not yet determined the heritability of uric acid levels in GOCADAN, nor its potential linkage with genes for its putative renal tubular transporters.

Strengths of this study include the large representative sample, systematic and standardized measures, and availability of many key covariates. This population of Alaska Eskimos differs strikingly from American Indian tribal populations in that there is a much lower burden of both diabetes and CKD. Even though recruitment was population-based, the study group was comprised of several large inter-related families; still, when we accounted for relatedness in our analyses, our results did not change.[30] Further studies are needed to explore the heritability and genetic influences on serum uric acid in this population.

Limitations include the cross-sectional analysis and the use of a single measurement of eGFR rather than the two measurements more than 90 days apart as recommended in clinical guidelines.[26] We were unable to account for any history of gout. Additionally, we could not account for dietary factors, such as fructose, that may increase uric acid levels.[49, 50] We did not have the power to further stratify by stages of CKD to explore associations in the more advanced stages.

In conclusion, in this population with lower than expected prevalence of diabetes but higher cardiovascular disease risk, uric acid was independently associated with both CKD and HTN. Prospective analyses are needed to determine whether it predicts incident disease as well studies that examine the effect of uric acid lowering on CKD and HTN.

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Table 1

Baseline Characteristics of GOCADAN Participants by Chronic Kidney Disease Status (n=1078)

Characteristics	No CKD (n = 1003)	CKD (n =75)	*p-value*
Sociodemographics			
Age, years, s.d.	41 (15)	63 (13)	<0.001
Males, n (%)	443 (44%)	23 (32%)	0.05
Education, years, s.d.	11.9 (2.2)	10.0 (4.1)	<0.001
Clinical Parameters			
Body Mass Index (kg/m^2), mean, s.d.	27.6 (5.9)	28.3 (5.0)	0.30
Obesity (BMI ≥ 30), n (%)	292 (29%)	27 (36%)	0.22
Diabetes, n (%)	29 (3%)	7 (9%)	0.003
Albuminuria, n (%)	59 (6%)	14 (20%)	<0.001
Hypertension, n (%)	183 (18%)	47 (63%)	<0.001
Systolic BP (mmHg), mean, s.d.	118 (14)	130 (19)	<0.001
Smoker, current or former, n (%)	817 (82%)	51 (68%)	0.004
Laboratory Values			
Total Cholesterol, mg/dL, mean, s.d.	199 (40)	215(44)	<0.001
HDL-C, mg/dL, mean, s.d.	59 (18)	63 (23	0.06
LDL-C, mg/dL, mean, s.d.	115 (35)	124 (37)	0.02
TG, mg/dL, geometric mean, (95% CI) *	111 (107–114)	124 (111–139)	0.06
Serum uric acid (mg/dL)	5.2 (1.2	6.5 (1.9)	<0.001
hsCRP, mg/dL, geometric mean, (95% CI) *	0.9 (0.8–1.7)	1.2 (0.8–1.7)	0.23
eGFR (mL/min per 1.73m^2) MDRD, mean, s.d.	89 (16)	51 (9)	<0.001

* Note: p-value is performed using log-transformed variables for Trigylcerides (TG) and high sensitivity C reactive protein (hsCRP).

Table 2

Association of Sociodemographics, Clinical Factors, and Labs with Increasing Tertiles of Uric Acid (UA) among GOCADAN Participants (n=1078)

	UA≤4.6 Tertile 1 (n=384)	**4.7≤UA ≤5.7 Tertile 2 (n=344)**	**5.8≤UA≤11.8 Tertile 3 (n=350)**	***p-value for trend***
Sociodemographics				
Age, years, s.d.	39 (14)	43 (15)	46 (18)	<0.001
Males, n (%)	73 (19%)	159 (46%)	234 (67%)	<0.001
Clinical Parameters				
Body Mass Index (kg/m^2), mean, s.d.	26.4 (5.1)	27.8 (6.0)	28.9 (6.2)	<0.001
Obesity (BMI ≥ 30), n (%)	93 (24%)	100 (29%)	126 (36%)	<0.001
Diabetes, n (%)	7 (2%)	12 (4%)	17 (5%)	0.02
Albuminuria, n (%)	21 (6%)	22 (7%)	30 (9%)	0.09
With Hypertension (n=221)	7 (15%)	7 (12%)	23 (20%)	0.35
Without Hypertension (n=818)	14 (4%)	15 (6%)	7 (3%)	0.64
Hypertension, n (%)	47 (12%)	60 (17%)	123 (35%)	<0.001
Systolic blood pressure (mmHg), mean, s.d.	115 (14)	119 (14)	123 (15)	<0.001
Smoker, current or former, n (%)	314 (82%)	285 (83%)	269 (77%)	0.14
Laboratory Values				
Triglycerides, mg/dL, mean, s.d.	110 (69)	123 (73)	154 (111)	<0.001
hsCRP (mg/dL), mean, s.d.	2.4 (7.3)	3.7 (8.8)	3.4 (7.6)	<0.001
eGFR (mL/min per 1.73m^2), mean, s.d.	92 (18)	88 (17)	79 (19)	<0.001
eGFR <60 mL/min per 1.73m^2, n (%)	12 (3%)	15 (4%)	48 (14%)	<0.001

Note about the statistical test:
p-values in Table 2 are based on a nonparametric trend test performed using Stata 11 (nptrend). It is a test for trend across ordered groups and is an extension of the Wilcoxon rank-sum test (ranksum). A correction for ties is also incorporated into the test.

Table 3

Logistic and Linear regression models examining the associations between uric acid and prevalent CKD among GOCADAN participants (N=1078) before and after adjustment of covariates.

	Odds Ratio (95% CI) CKD Dichotomized Uric acid continuous	Coefficient (95% CI) CKD Continuous Uric acid continuous
Model 1 – uric acid only (univariate)	1.82 (1.55–2.14) *	−4.66 (−5.44 to −3.88) *
Model 2 - including age, sex, smoking	1.77 (1.46–2.15) *	−4.44 (−5.20 to −3.68) *
Model 3 – above plus BMI, diabetes, trigylcerides	1.96 (1.57–2.46) *	−4.96 (−5.76 to −4.16) *
Model 4 – above plus systolic BP	1.96 (1.57–2.46) *	−4.97 (−5.78 to −4.18) *
Model 5 – above plus hsCRP	2.04 (1.62–2.56) *	−4.88 (−5.69 to −4.07) *

* p-value <0.05

Table 4

Baseline characteristics by prevalent HTN status. (N=1077)

	No HTN (n =847)	HTN (n = 230)	*p-value*
Sociodemographics			
Age, years, s.d.	39 (14)	57 (15)	<0.001
Males, n (%)	353 (42%)	113 (49%)	0.04
Education, years	12 (2)	11 (4)	<0.001
Clinical Parameters			
BMI (kg/m^2), mean, s.d.	27 (6)	30 (6)	<0.001
Obesity (BMI ≥ 30), n (%)	211 (25%)	108 (48%)	<0.001
Diabetes, n (%)	7 (1%)	29 (13%)	<0.001
Albuminuria, n (%)	36 (4%)	37 (17%)	<0.001
Smoker, current or former, n (%)	698 (82%)	169 (74%)	0.005
Laboratory Values			
Total Cholesterol, mg/dL, mean, s.d	199 (41)	204 (36)	0.07
HDL-C, mg/dL, mean, s.d.	60 (18)	59 (19)	0.60
LDL-C, mg/dL, mean, s.d.	115 (36)	115 (31)	0.79
TG, mg/dL, geometric mean, s.d.	120 (76)	160 (116)	<0.001*
Serum uric acid (mg/dL), mean, s.d.	5.1 (1.2)	6.0(1.6)	<0.001
hsCRP, geometric mean, s.d.	2.9 (8.4)	4.3 (8.4)	<0.001*
Estimated GFR (mL/min per 1.73m^2) MDRD	90 (17)	76 (19)	<0.001

*Note: p-value is performed using log-transformed variables for Trigylcerides (TG) and high sensitivity C reactive protein (hsCRP).

Table 5

Logistic regression models examining the associations between uric acid and prevalent HTN among GOCADAN participants (n=1077) before and after adjustment of covariates.

	Odds Ratio for uric acid (95% CI)
Model 1 – uric acid only (univariate)	1.71 (1.52–1.92) *
Model 2 - including age, sex, smoking	1.54 (1.34–1.78) *
Model 3 – above plus BMI, diabetes, triglycerides	1.32 (1.14–1.54) *
Model 4 – above plus eGFR	1.24 (1.06–1.46) *
Model 5 – above plus hsCRP	1.24 (1.06–1.46) *

* p-value <0.05