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Effect of Serum Insulin on the Association between Hyperuricemia and Incident Heart Failure

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Abstract

Elevated serum uric acid (UA) is associated with incident heart failure (HF). However, whether it is a direct effect of UA or an effect of increased xanthine oxidase (XO) is unknown. Because hyperuricemia in hyperinsulinemia is primarily due to impaired renal UA excretion, its association with incident HF would suggest a direct UA effect. In contrast, hyperuricemia in normoinsulinemia is likely due to increased UA production and thus its association with incident HF would suggest an XO effect. To clarify this, we examined the association of hyperuricemia with centrally-adjudicated incident HF in Cardiovascular Health Study participants with and without hyperinsulinemia. Of the 5,411 participants ≥ 65 years without baseline HF, 1491 (28%) had hyperuricemia (serum UA ≥ 6 mg/dL for women and ≥ 7 mg/dL for men). Propensity scores for hyperuricemia were estimated using 63 baseline characteristics. Mean serum UA was 6.0 and 5.3 mg/dL in those with ($n=2,731$) and without ($n=2,680$) hyperinsulinemia (≥ 13 mU/L, median serum insulin) respectively ($p<0.001$). Propensity-adjusted hazard ratios (95% confidence intervals) for hyperuricemia-associated incident HF during 8 years of median follow-up were 0.99 (0.83–1.18; $p=0.886$) and 1.32 (1.04–1.67; $p=0.021$) for those with and without hyperinsulinemia respectively (p for interaction, 0.014). In conclusion, the absence of an association of hyperuricemia with incident HF among those with hyperinsulinemia (despite a significantly higher mean serum UA) and a significant association in normoinsulinemia suggest that UA has no intrinsic association with incident HF and that it may predict incident HF when it is a marker of increased of XO activity.

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Conflict of Interest Disclosures: None

Keywords

Uric acid; insulin; incident heart failure; older adults

Elevated serum uric acid (UA) is associated with increased risk of heart failure (HF) and cardiovascular morbidity.¹⁻³ However, whether hyperuricemia-associated poor cardiovascular outcomes are due to a direct effect of UA or due to an underlying increased xanthine oxidase (XO) activity is unclear. Hyperinsulinemia has been shown to be associated with impaired renal UA clearance.^{4, 5} Therefore, it is likely that in those with hyperinsulinemia, serum UA may be elevated due to decreased elimination of UA rather than its increased production. Thus, an association of hyperuricemia and incident HF in those with hyperinsulinemia will likely represent a direct effect of UA. On the contrary, hyperuricemia in those with normoinsulinemia is more likely to be due to increased UA production, and thus a marker of increased XO activity. Thus, an association of hyperuricemia with incident HF in those with normoinsulinemia will likely represent an effect of XO. Because XO activity is a known cause of oxidative stress^{6, 7} while UA is known for its anti-oxidant properties,^{8, 9} we hypothesized that hyperuricemia-associated increase in incident HF² will be observed in those with normoinsulinemia but not in those with hyperinsulinemia. To test this hypothesis, we examined the association of hyperuricemia and incident HF in a cohort of community-dwelling older adults with and without hyperinsulinemia.

Methods

For the current study, we used de-identified public-use copies of the Cardiovascular Health Study (CHS) datasets. The rationale, design, and implementation of the CHS have been previously detailed.^{10, 11} Briefly, CHS is an ongoing prospective epidemiologic study of 5,888 Medicare-eligible community-dwelling adults ≥ 65 years recruited from four US counties. National Heart, Lung, and Blood Institute sponsored the CHS and also provided the current datasets, which include 5,795 participants (93 did not consent to be included in the public-use datasets). Of these, we excluded 255 participants with centrally-adjudicated prevalent HF at baseline, 79 participants without data on baseline serum UA and 50 participants without data on baseline serum insulin. The final sample size for the current analysis was 5,411.

Serum UA levels were measured in a central blood analysis laboratory using Kodak Ektachem 700 analyzer assay (Eastman Kodak, Rochester, NY).^{2, 12} Based on commonly-used gender-based cut-offs, we defined hyperuricemia as serum UA levels ≥ 6 mg/dL for women and ≥ 7 mg/dL for men.^{2, 3} Serum insulin levels were measured by a competitive radioimmunoassay (Diagnostic Products Corp, Malvern, PA).^{12, 13} Serum insulin levels ≥ 13 mU/L (median value) was used to define hyperinsulinemia. Of the 5,411 participants, 2,731 had hyperinsulinemia and 2,680 had normoinsulinemia. Data on socio-demographic, clinical, sub-clinical, and laboratory variables were collected at baseline and have been previously described in details.^{10, 11}

The primary outcome for this study was definite new-onset HF. The process of adjudication of HF in CHS has been very well documented in the literature.^{11, 14, 15} Briefly, participants were asked about self-reports of a physician diagnosis of HF during semi-annual visits. The CHS Events Committee later adjudicated the diagnosis of HF through the examination of participant's medical records for evidence suggestive of HF, and follow up surveillances.

For descriptive analyses, we used Pearson Chi-square and Student t-tests as appropriate. We used a non-parsimonious multivariable logistic regression model to estimate propensity scores for hyperuricemia (for each of the 5,411 participants), which is the conditional probability of having hyperuricemia given a set of measured baseline characteristics.^{16, 17} In the model hyperuricemia was the dependent variable and 63 baseline characteristics and a significant interaction term (between age and baseline serum creatinine) were covariates. To determine if the association between hyperuricemia and incident HF varied by the presence of hyperinsulinemia, we formally tested for two-way interaction using a Cox regression model. In the model, incident HF was the dependent variable, and hyperuricemia and hyperinsulinemia were entered as main effect terms, along with an interaction term for the two. To determine the independence of the interaction between hyperuricemia and hyperinsulinemia, we adjusted the model for propensity score, which is a composite score for the 63 measured baseline characteristics. To determine the association between hyperuricemia and incident HF in those with and without hyperinsulinemia, we then repeated our Cox regression model separately in those groups. All statistical tests were two-sided, and tests with p-value <0.05 were considered significant. Confidence intervals (CI) were computed based on a 95% confidence levels. SPSS for Windows (Rel. 15. 2006. Chicago: SPSS Inc.) was used for all data analysis.

Results

Our study cohort had a mean age 73 (± 6) years; 58% were women and 15% were African American. The baseline characteristics by hyperuricemia, among those with and without hyperinsulinemia are displayed in Table 1. The prevalence of hyperuricemia was 18% (470/2680) and 37% (1021/2731) among those with normoinsulinemia and hyperinsulinemia respectively. The mean $\pm$ SD serum UA (6.0 ± 1.5 versus 5.3 ± 1.4 mg/dL; $p < 0.001$), creatinine (1.0 ± 0.4 versus 0.9 ± 0.4 mg/dL; $p < 0.001$) and insulin (24.0 ± 33.0 versus 9.2 ± 2.0 μ IU/mL; $p < 0.001$) levels were higher for those with hyperinsulinemia than those without.

Among participants with normoinsulinemia, incident HF developed in 26% and 17% of those with and without hyperuricemia (unadjusted hazard ratio {HR} when hyperuricemia was compared with normouricemia, 1.80; 95% CI, 1.47–2.21; $p < 0.001$; Figure 1a and Table 2). In the hyperinsulinemia group, incident HF occurred in 26% and 21% of those with and without hyperuricemia (unadjusted HR when hyperuricemia was compared with normouricemia, 1.34; 95% CI, 1.15–1.57; $p < 0.001$; Figure 1b and Table 2). This association was significantly different in those with and without hyperinsulinemia (p for interaction, 0.025; Table 2).

After adjustment for propensity scores, the association between hyperuricemia and incident HF was significant only among participants with normoinsulinemia (adjusted HR when hyperuricemia was compared with normouricemia, 1.32; 95% CI, 1.04–1.67; $p = 0.021$) but not among those with hyperinsulinemia (adjusted HR when hyperuricemia was compared with normouricemia, 0.99; 95% CI, 0.83–1.18; $p = 0.886$; adjusted p for interaction, 0.014; Table 2).

Discussion

The findings from the current analysis demonstrate that hyperuricemia-associated increased risk of new-onset HF was significantly higher in community-dwelling older adults with normoinsulinemia than in those with hyperinsulinemia. The lack of an intrinsic association between hyperuricemia and incident HF among those with hyperinsulinemia, despite a higher prevalence of hyperuricemia and a significantly higher mean serum UA level, supports our hypothesis that UA has no intrinsic association with incident HF. Because

unlike in hyperinsulinemia, renal excretion of UA is not impaired in normoinsulinemia, hyperuricemia in those individuals would be expected to be due to increased UA production. Therefore, a significant association of hyperuricemia and incident HF among those with normoinsulinemia suggest that hyperuricemia may predict incident HF when it is a marker of increased XO activity, thus further lending support to our hypothesis of a lack of an intrinsic effect of UA on incident HF.

Because hyperinsulinemia is known to be associated with impaired renal UA excretion, hyperuricemia in this group is likely to be due to retention of UA rather than increased production alone.^{4, 5} This is also supported by our observation that the prevalence of hyperuricemia was twice higher with a significantly higher mean serum UA level in those with hyperinsulinemia than in those with normoinsulinemia. Hyperuricemia in those with normoinsulinemia, on the other hand, is less likely due to impaired renal UA excretion and more likely to be due to increased UA production. Although we had no data on XO activity, it may be reasonable to infer that hyperuricemia in those with normoinsulinemia is a marker of increased XO activity, which is a known cause of oxidative stress.^{6, 7} Although XO inhibition has been shown to improve cardiac remodeling, cardiac energetics, and endothelial function,^{18, 19} it has not been shown to improve outcomes in patients with advanced HF.²⁰ Findings from the currently analysis may provide insights into why the beneficial effects of XO inhibition may not have translated into better outcomes in human HF.^{20, 21} XO inhibition may not be effective in improving outcomes when hyperuricemia is not a marker of increased XO activity.

Although acute systemic administration of UA has been shown to improve endothelial function,⁸ less is known regarding the effect of chronic elevation of UA in humans.^{9, 22} A closer examination of the findings from the current study may support the notion of a beneficial effect of an elevated serum UA level. Participants with hyperinsulinemia would have a similar prevalence of hyperuricemia (37%), mean UA level (6 mg/dL) and increase in hyperuricemia-associated HF risk (32%) if they had normal renal UA excretion as in normoinsulinemia. If UA had an intrinsic effect on incident HF, then the higher prevalence of hyperuricemia with a higher mean UA level caused by renal retention of UA in those with hyperinsulinemia would be expected to further increase the risk of HF in that group. The lack of such an increase in the intrinsic association between UA and incident HF in those with hyperinsulinemia suggests that hyperuricemia caused by renal retention of UA may have eliminated the risk of HF associated with hyperuricemia caused by XO activity. Therefore, the lack of an association of hyperuricemia and incident HF in those with hyperinsulinemia may actually point to a beneficial effect of UA rather than a neutral effect of UA.

Our study has several limitations. We had no data on history of gout or the baseline use of XO inhibitors. We also had no data on serum UA during follow-up, levels of which may have changed. However, any potential underestimation due to such regression dilution would be expected to be similar in those with and without hyperinsulinemia.²³ In conclusion, the findings of this study suggest that despite a higher prevalence of a more pronounced hyperuricemia in those with hyperinsulinemia, there was no association between hyperuricemia and incident HF. Taken together with the significant association between hyperuricemia and incident HF in normoinsulinemia, these findings suggest that UA has no intrinsic association with incident HF and that it may predict incident HF only when it is a marker of increased of XO activity. The findings of the current study needs to be replicated in other populations, and future studies need to test the effectiveness of XO inhibition in reducing the risk of incident HF in at-risk populations with hyperuricemia in the presence of normal renal UA excretion.

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Figure 1.
Kaplan-Meier plots for hyperuricemia-associated incident heart failure by serum insulin levels

Table 1

Baseline characteristics of community-dwelling older adults with and without hyperuricemia* in subgroups with serum insulin level < and ≥ the median value of 13 mU/L

Variable	Serum insulin level <13 mU/L			Serum insulin level ≥13 mU/L		
	Normouricemia (n=2210)	Hyperuricemia (n=470)	p Value	Normouricemia (n=1710)	Hyperuricemia* (n=1021)	p Value
Age (years)	73 ± 6	75 ± 6	<0.001	73 ± 5	73 ± 6	0.101
Female	1300 (59%)	258 (55%)	0.117	948 (55%)	611 (60%)	0.024
African American	335 (15%)	81 (17%)	0.259	216 (13%)	166 (16%)	0.008
Current smoker	295 (13%)	51 (11%)	0.143	194 (11%)	115 (11%)	0.948
Alcohol intake (units per week)	3 ± 6	4 ± 9	0.001	2 ± 6	2 ± 6	0.498
Body mass index (kg/m ²)	25 ± 3	26 ± 4	<0.001	28 ± 4	29 ± 4	<0.001
Self-reported general health	408 (19%)	124 (26%)	<0.001	426 (25%)	305 (30%)	0.005
Comorbidities						
Hypertension	1086 (49%)	306 (65%)	<0.001	1006 (59%)	749 (73%)	<0.001
Acute myocardial infarction	121 (6%)	53 (11%)	<0.001	167 (10%)	95 (9%)	0.692
Diabetes mellitus	137 (6%)	40 (9%)	0.067	414 (24%)	238 (23%)	0.593
Chronic kidney disease	283 (13%)	193 (41%)	<0.001	272 (16%)	386 (38%)	<0.001
Stroke	57 (3%)	29 (6%)	<0.001	66 (4%)	51 (5%)	0.156
Atrial fibrillation	42 (2%)	11 (2%)	0.534	34 (2%)	27 (3%)	0.262
Clinical findings						
Pulse (beats per minute)	66 ± 11	67 ± 11	0.231	69 ± 11	69 ± 11	0.282
Systolic blood pressure (mm Hg)	135 ± 22	139 ± 23	<0.001	137 ± 21	138 ± 21	0.621
Diastolic blood pressure (mm Hg)	70 ± 11	71 ± 11	0.189	71 ± 11	71 ± 12	0.390
Medications						
Angiotensin-converting enzyme inhibitors	104 (5%)	31 (7%)	0.089	123 (7%)	87 (9%)	0.208
Beta-blocker	203 (9%)	80 (17%)	<0.001	214 (13%)	193 (19%)	<0.001
Aspirin	59 (3%)	13 (3%)	0.907	70 (4%)	25 (2%)	0.023
Statin	42 (2%)	7 (2%)	0.546	43 (3%)	29 (3%)	0.607
Non-steroidal anti-inflammatory drugs	250 (11%)	74 (16%)	0.007	199 (12%)	162 (16%)	0.002
Loop diuretics	41 (2%)	36 (8%)	<0.001	71 (4%)	109 (11%)	<0.001

Variable	Serum insulin level <13 mU/L			Serum insulin level ≥13 mU/L		
	Normouricemia (n=2210)	Hyperuricemia (n=470)	p Value	Normouricemia (n=1710)	Hyperuricemia* (n=1021)	p Value
Thiazide diuretics	157 (7%)	73 (16%)	<0.001	176 (10%)	205 (20%)	<0.001
Serum chemistry tests						
Uric acid (mg/dL)	4.8 ± 1.0	7.3 ± 1.0	<0.001	5.1 ± 0.9	7.5 ± 1.1	<0.001
Glucose (mg/dL)	101 ± 26	104 ± 23	0.068	120 ± 44	118 ± 40	0.474
Insulin (mU/L)	9 ± 2	10 ± 2	<0.001	24 ± 33	25 ± 31	0.375
Creatinine (mg/dL)	0.9 ± 0.3	1.1 ± 0.5	<0.001	0.9 ± 0.4	1.1 ± 0.4	<0.001
Potassium (mEq/L)	4.2 ± 0.3	4.2 ± 0.4	0.259	4.2 ± 0.4	4.1 ± 0.4	<0.001
Cholesterol (mg/dL)	210 ± 37	218 ± 42	<0.001	211 ± 38	215 ± 43	0.010
Low-density lipoprotein (mg/dL)	128 ± 34	134 ± 37	<0.001	131 ± 40	133 ± 40	0.091
High-density lipoprotein (mg/dL)	59 ± 16	56 ± 17	0.001	51 ± 14	49 ± 13	<0.001
Triglyceride (mg/dL)	116 ± 51	135 ± 68	<0.001	151 ± 90	174 ± 87	<0.001
Albumin (g/dL)	4.0 ± 0.3	4.0 ± 0.3	0.406	4.0 ± 0.3	4.0 ± .3	<0.001
Fibrinogen (mg/dL)	314 ± 63	323 ± 65	0.003	325 ± 66	337 ± 69	<0.001
Interleukin (pg/dL)	1.9 ± 1.7	2.2 ± 1.8	0.001	2.2 ± 1.7	2.6 ± 2.1	<0.001
C-reactive protein (mg/L)	3.6 ± 6.3	5.1 ± 7.6	<0.001	5.0 ± 9.7	6.1 ± 8.6	0.002
Left ventricular hypertrophy by electrocardiogram	78 (4%)	29 (6%)	0.008	61 (4%)	63 (6%)	0.002

* Hyperuricemia is defined as serum uric acid levels ≥6 mg/dL for women and ≥7 mg/dL for men

Table 2

Associations of hyperuricemia* with incident heart failure in subgroups of community-dwelling older adults with serum insulin level < and $\geq$ the median value of 13 mU/L

	Serum insulin level <13 mU/L		Serum insulin level $\geq$ 13 mU/L		Interaction p Value
	Normouricemia (n=2210)	Hyperuricemia (n=470)	Normouricemia (n=1710)	Hyperuricemia* (n=1021)	
Incident heart failure: n (%)	370 (17%)	122 (26%)	361 (21%)	267 (26%)	---
Unadjusted hazard ratio (95% CI)	1.00 (Reference)	1.80 (1.47–2.21); P <0.001	1.00 (Reference)	1.34 (1.15–1.57) P <0.001	0.025
Propensity score-adjusted hazard ratio (95% CI)	1.00 (Reference)	1.32 (1.04–1.67); P =0.021	1.00 (Reference)	0.99 (0.83–1.18) P =0.886	0.014

* Hyperuricemia is defined as serum uric acid levels $\geq$ 6 mg/dL for women and $\geq$ 7 mg/dL for men