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The association between serum ferritin and uric acid in humans

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Abstract

Objective: Urate forms a coordination complex with Fe^{3+} which does not support electron transport. The only enzymatic source of urate is xanthine oxidoreductase. If a major purpose of xanthine oxidoreductase is the production of urate to function as an iron chelator and antioxidant, a system for coupling the activity of this enzyme to the availability of catalytically-active metal would be required. We tested the hypothesis that there is an association between iron availability and urate production in healthy humans by correlating serum concentrations of ferritin with uric acid levels.

Materials and methods: The study population included 4932 females and 4794 males in the National Health and Nutrition Examination Survey III. They were 20 years of age or older and in good health.

Results: Serum concentrations of ferritin correlated positively with uric acid levels in healthy individuals ($R^2 = 0.41$, $p < 0.001$). This association was independent of an effect of gender, age, race/ethnic group, body mass, and alcohol consumption.

Conclusions: The relationship between serum ferritin and uric acid predicts hyperuricemia and gout in groups with iron accumulation. This elevation in the production of uric acid with increased concentrations of iron could possibly reflect a response of the host to diminish the oxidative stress presented by available metal as the uric acid assumes the empty or loosely bound coordination sites of the iron to diminish electron transport and subsequent oxidant generation.

Keywords: *Xanthine oxidase, iron, phlebotomy, oxidants, gout*

Introduction

While most mammals possess urate oxidase to degrade uric acid to allantoin, humans lack this enzyme. As a result, uric acid is the end product of purine metabolism in humans and concentrations in extracellular fluids approach the saturation point of the compound (approximately 7 mg/dl). The purpose of urate has not been defined but it can function as an antioxidant by scavenging singlet oxygen, hydroxyl radicals, oxoheme oxidants, hydroperoxyl radicals, and hypochlorous acid [1]. In addition, urate can form a 2:1 complex with Fe^{3+} ions with an overall stability constant (K_{sc}) of 1.1×10^{11} [2]. This coordination complex does not appear to support electron transport and therefore, urate inhibits iron-catalyzed oxidations [3].

The only enzymatic source of urate is xanthine oxidoreductase. If a major purpose of xanthine oxidoreductase is the production of urate to function as an iron chelator and antioxidant, a system for coupling the activity of this enzyme to the availability of catalytically-active metal would be required.

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In cultured cells, the activity and expression of xanthine oxidoreductase have been demonstrated to increase following exposures to iron [4,5]. In further support of a possible association between levels of iron and urate, exposures of both rodents [6,7] and humans [8] to elevated concentrations of this metal increase urate in contrast to all other antioxidants which are decreased. We tested the hypothesis that there is an association between iron availability and urate production in healthy humans by correlating serum concentrations of ferritin with uric acid levels. An association between urate and ferritin would imply a potential for both hyperuricemia and gout in groups with iron accumulation.

Materials and methods

Between 1988 and 1994, a sample of the non-institutionalized, civilian population in the United States was selected using a multistage, stratified sampling design. These individuals participated in the Third National Health and Nutrition Examination Survey (NHANES III). After being interviewed at home, survey participants were invited for an examination and additional interviews. For most participants, blood was drawn at the examination clinic but for some who were unable to attend because of health reasons, a blood sample was obtained during the home interview. Details about the survey and its methods have been previously published [9,10].

NHANES III participants attended one of three examination sessions: morning, afternoon, or evening. Those attending the morning sessions were asked to fast for 10–16 h. Those attending the afternoon and evening sessions were asked to fast for at least 6 h.

A potential source of metal to present an oxidative stress to a living system is that bound by storage and transport proteins [11]. Serum ferritin concentrations have been previously demonstrated to correlate linearly to body iron stores and reflect total metal accumulation in humans [12,13]. Serum ferritin concentration was measured using the Quantimmune IRMA kit (BioRad Laboratories, Hercules, California). Iron binding capacity and transferrin saturation, which are other indirect measures reflecting iron metabolism, were also measured using an automated colorimetric method. Uric acid was measured on a Hitachi Model 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Details of blood measures including quality assurance have been previously described [14].

Variables used in the analysis included gender, age, race or ethnicity, body mass index, and alcohol consumption. Body mass index was calculated from measured weight and height (weight in kilograms divided by height in meters squared). Alcohol use was estimated by summing the reported frequency of drinking beer, wine, or hard liquor during the prior month from questions that were asked on the food frequency questionnaire.

Analyses were limited to participants who were 20 years or older. In addition, participants who reported having had one of the following conditions were excluded: arthritis, myocardial infarction, angina pectoris, congestive heart failure, stroke, cancer, asthma, bronchitis, emphysema, or lupus. Pearson correlations for the ranks of ferritin concentration with uric acid concentration were calculated in SAS. In addition, multiple linear regression analysis of ferritin concentration on uric acid concentration was performed. To account for the complex survey design, SUDAAN was used to produce our weighted estimates and standard errors [15].

Results

The study population included 4932 females and 4794 males with the age ranging from 20 to over 90 years. Characterization of the group by race/ethnicity is provided (Table I). Mean serum ferritin and uric acid concentrations were greater for males relative to females for all races/ethnic groups ($p < 0.001$ for all comparisons). Comparable to previous investigations [16–18], African–Americans demonstrated higher concentrations of both ferritin and uric acid. African–American females had significantly higher ferritin levels relative to both white ($p = 0.003$) and Mexican–American females ($p < .001$). Furthermore, white females had higher ferritin concentrations than Mexican–American females ($p < 0.001$). Similarly, African–American men had higher ferritin concentrations than both white ($p < 0.001$) and Mexican–American males ($p < 0.001$). Among the values of serum uric acid concentrations, only that comparison between female African–Americans and Mexican–Americans reached significance ($p = 0.002$).

Table I. Serum ferritin and uric acid concentrations for genders and racial/ethnic groups (mean +/− standard error).

	Women			Men		
	n	Uric acid (Φmol/l)	Ferritin (Φg/l)	*n*	Uric acid (Φmol/l)	Ferritin (Φg/l)
White	1790	263.5 ∀ 2.2	69.0 ∀ 2.0	1662	355.6 ∀ 2.3	171.7 ∀ 4.5
African–American	1418	269.8 ∀ 2.6	79.4 ∀ 3.1	1306	360.4 ∀ 2.6	208.0 ∀ 6.4
Mexican–American	1484	258.0 ∀ 2.8	53.4 ∀ 2.0	1625	357.5 ∀ 2.7	163.2 ∀ 3.6
Other	240	269.9 ∀ 6.4	71.5 ∀ 9.7	201	362.9 ∀ 5.5	180.6 ∀ 15.5

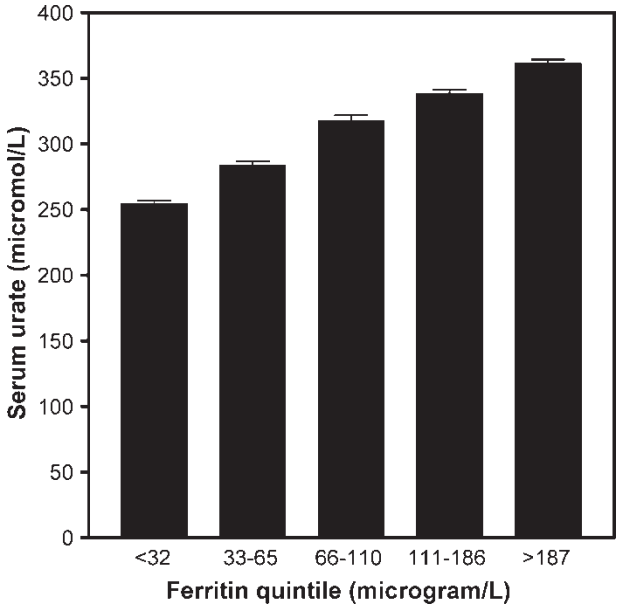

Figure 1. Mean serum urate concentrations for 9726 individuals without evidence of any chronic condition. These are means +/− standard error provided at the quintile ferritin values.

Prior to controlling for an effect of any variable, there was a significant association of serum ferritin with urate levels with correlation coefficient value of 0.48 ($p < 0.0001$). Concentrations of urate rose linearly as ferritin increased (Figure 1). After adjustment for gender, age, race/ethnicity, body mass index, and number of drinks per month, ferritin was found to contribute to the variability of serum uric acid in regression analysis (Table II). To support an association between iron metabolism and urate production, the regression was repeated but iron binding capacity and then transferrin saturation were employed rather than serum ferritin. Both iron binding capacity and transferrin saturation also demonstrated statistically significant associations with serum uric acid (Table III).

Obesity effects both ferritin and uric acid levels with elevations of both in overweight individuals [19,20]. Increased values of body mass index were associated with greater concentrations of both uric acid and ferritin in the serum (Table IV). Both before and after adjustment for gender (except in gender-specific models), age, race/ethnicity, and number of alcoholic drinks/month, there were significant correlations between serum concentrations of ferritin and uric acid among individuals included in all three groups defined by body mass (18.5 to <25, 25 to <30, and >30 kg/m^2) (Table IV).

Table II. Regression of serum ferritin concentrations onto uric acid levels in healthy subjects.

	n	Regression coefficient (∃)	R^2	*p*
Women	4919	0.1112	0.23	0.001
Men	4785	0.0471	0.12	0.002
Total	9704	0.6788	0.41	<0.001

Adjusted for gender (except gender-specific data), age, race/ethnicity, body mass index, and alcohol consumption.

Table III. Regression of iron binding capacity and transferrin saturation onto uric acid levels in healthy subjects.

	n	R^2	*p*
Iron binding capacity (Φmol/l)	9690	0.40	0.006
Transferrin saturation (%)	9683	0.40	<0.001

Adjusted for gender, age, race/ethnicity, body mass index, and alcohol consumption.

Comparable to obesity, alcohol consumption can increase serum ferritin and uric acid [21,22]. Prior to adjustment for gender (except in gender-specific models), age, race/ethnicity, and body mass, those individuals consuming a greater number of alcoholic drinks were noted to have higher values of both serum ferritin (113.1, 127.4, and 210.4 Φg/ml for no drinks, 1–2 drinks, and >3 drinks/day, respectively) and uric acid (300.8 +/− 2.0, 317.0 +/− 1.9, and 357.3 +/− 8.2 Φmol/l for no drinks, 1–2 drinks, and >3 drinks/day, respectively). Before adjustment, there were significant correlations between serum concentrations of ferritin and uric acid among individuals included in all three groups defined by consumption of alcoholic drinks. However, this relationship between ferritin and uric acid among groups defined by consumption of alcoholic drinks was lost after adjustment for these variables (Table V).

Discussion

In the regression model, ferritin significantly contributed to the variation of uric acid levels independent of any effect of gender, age, race/ethnicity, body mass index, and number of alcoholic drinks per day. Differences in serum uric acid levels between genders have been attributed to an enhancing effect of estrogens on renal urate clearance [23]. However, uric acid concentrations increase in females after menopause even among those receiving estrogen replacement therapy. The correlation between ferritin and uric acid concentrations delineated in this study suggests that elevations in available iron which follow cessation of menses in females could elevate xanthine oxidoreductase activity and consequently influence uric acid concentrations. Similarly, the process of aging is one of iron accumulation in normal subjects reflected by elevations in ferritin [24]. This increased availability of metal would elevate uric acid again by affecting the activity of xanthine oxidoreductase. Finally, elevations in serum ferritin levels in African–Americans, those with greater body mass, and alcoholics suggest some disparity (or disparities) in iron metabolism among these groups. These are

Table IV. Regression of serum ferritin concentrations onto uric acid levels after stratification of the study population by body mass index.

	Body mass index														
	18.5 to $<25\,kg/m^2$					25 to $<30\,kg/m^2$					$\geq 30\,kg/m^2$				
	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	P	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	p	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	p
Women	1998	64.3	243.8	0.07	.005	1467	72.8	273.4	0.11	.002	1321	78.3	307.0	0.06	.059
Men	1891	162.3	336.2	0.04	.022	1939	176.2	362.8	0.02	.001	903	207.8	394.8	0.04	.294
Total	3889	114.6	290.8	0.40	.002	3406	124.8	318.7	0.28	$<.001$	2224	142.3	351.2	0.28	.042

Adjusted for gender (except gender-specific data), age, race/ethnicity, and alcohol consumption.

Table V. Regression of serum ferritin concentrations onto uric acid levels after stratification of the study population by consumption of alcohol.

	Alcohol intake														
	None					1 to 2 drinks/day					≥ 3 drinks/day				
	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	p	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	p	n	Mean ferritin (Φg/l)	Mean urate (Φmol/l)	R^2	p
Women	2890	69.6	264.7	0.22	0.015	2000	68.8	264.4	0.26	<0.001	29	152.5	258.5	–*	–*
Men	1639	160.9	354.1	0.12	0.033	2979	180.7	359.3	0.12	0.04	167	212.4	336.7	0.27	0.099
Total	4529	116.9	310.3	0.37	<0.001	4979	126.3	312.8	0.43	0.001	196	167.1	290.0	0.30	0.031

Adjusted for gender (except gender-specific data), age, race/ethnicity, and body mass index.
*Women consuming ≥ 3 drinks/day provide an insufficient sample size to evaluate independently.

the same groups which can exhibit elevated serum uric acid levels and the greater availability of iron (as reflected by elevations in ferritin) may be participating in this increase of serum uric acid.

Alcohol consumption has previously been demonstrated to elevate serum uric acid values [21]. The failure of number of alcoholic drinks per day to affect serum concentrations of uric acid and ferritin after adjustment for gender, age, race/ethnicity, and body mass in this study, may reflect its colinearity with one or more of these independent variables.

In addition to contributing to an understanding of the influence of gender, age, race/ethnicity, body mass, and alcohol consumption on serum uric acid concentrations, the association between ferritin and uric acid could assist in defining other risk factors for hyperuricemia and gout. Ingested heme elevates iron in the serum of humans within minutes or hours of its consumption [25] and the effect of meat consumption on the exacerbation of gout may be ascribed to the effect of available iron on xanthine oxidoreductase rather than purine metabolism. In addition, the association between iron and uric acid described in this study predicts that individuals with evidence of either acute or chronic iron accumulation will be at increased risk for both hyperuricemia and gout. This might include patients with hemolytic anemia, myeloproliferative disease, tumor lysis syndrome, polycythemia vera, psoriasis, lymphoma, leukemia, malignancy, thalassemia, trauma, and rhabdomyolysis. Individuals treated with chemotherapy, radiation, and surgery, particularly transplantation, also exhibit a disequilibrium in iron metabolism with an accumulation of metal. This elevation in available iron could influence xanthine oxidoreductase activity and result in an increased production of uric acid and exacerbation of gout observed in these groups. Finally, elevated enzyme activity following increases in available iron could contribute to a mechanism for delineating saturnine gout since lead exposure can also be associated with both a disruption in iron metabolism [26] and an oxidative stress [27].

One limitation of this study is the potential for ferritin to function as an acute phase reactant reflecting inflammation rather than body iron stores. However, the study population was selected excluding any recognized inflammatory condition. In addition, when iron binding capacity and transferrin saturation were included in the regression rather than ferritin, a comparable association between the index of iron metabolism and urate levels was defined. This supports a relationship between urate production and metal metabolism rather than inflammation.

The specific mechanism mediating an increase in xanthine oxidoreductase activity following exposure to elevated concentrations of iron is unclear but numerous possibilities exist. There are a number of the conserved loop sequences C–A–G–U/A–G–U/C/A [28] of potential iron regulatory elements (IRE) within the published cDNA sequences for human xanthine dehydrogenase [29]. Therefore, similar to the post-transcriptional control of ferritin synthesis [30], the regulation of this enzyme may be through a short-lived repressor protein. Alternatively, iron-mediated generation of reactive oxygen species could promote a conversion of the dehydrogenase to the oxidase form of the enzyme by reversible sulfhydryl oxidation. Thirdly, xanthine oxidoreductase activity can be induced by tumor necrosis factor (TNF), interferon-α (IFN-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) [31]. Thus, increased xanthine oxidoreductase activity after increases in iron could represent upregulation of enzyme activity in response to a generation of reactive oxygen species, activation of transcriptional factors such as nF-κB and AP-1, and the consequent elevations of mediators after the binding of these factors in their promotor regions. TNF, IFN-α, IL-1 and IL-6 would then transcriptionally increase mRNA for xanthine oxidoreductase. Finally, nitric oxide ($NO^{\cdot}$) binds to iron–sulfur clusters or sulfhydryl groups of xanthine oxidoreductase, inhibiting its activity [32], and this inhibition is reversed by iron chelates such as hemoglobin [32]. $NO^{\cdot}$ has therefore been proposed as an endogenous regulatory inhibitor of xanthine oxidoreductase activity [32]. Increasing the cellular pool of iron could result in scavenging of $NO^{\cdot}$ by formation of iron–nitrosyl complexes [32], thereby releasing xanthine oxidoreductase from inhibition.

We conclude that serum concentrations of ferritin correlated positively with uric acid levels in healthy individuals. This association was independent of an effect of gender, age, race/ethnic group, body mass, and alcohol consumption. The relationship between the two predicts hyperuricemia in groups with iron accumulation. This elevation in the production of uric acid with increased concentrations of iron could possibly reflect a response of the host to diminish the oxidative stress presented by available metal with the uric acid assuming empty or loosely bound coordination sites of the iron to diminish electron transport and subsequent oxidant generation. The treatment of hyperuricemia might therefore include blood donation, as previously recommended [33], in addition to weight loss and avoidance of both alcohol and foods with abundant iron.

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