ORIGINAL RESEARCH

Uric Acid as a Potential Cue to Screen for Iron Overload

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Background: **It is suggested that targeted screening for hemochromatosis and iron overload may be worthwhile. The aim of this study was to examine uric acid as a potential indicator of the presence of iron overload.**

Methods: **We analyzed adults aged 20 and older in the National Health and Nutrition Examination Survey 1999 to 2002. We computed logistic regressions controlling for age, sex, race/ethnicity, liver or kidney condition, and alcohol use to see the relationship between combinations of uric acid and ferritin with the outcomes of elevated liver enzymes and proteinuria.**

Results: **In unadjusted analyses, 20.7% of individuals with high uric acid had high ferritin levels versus 8.8% of individuals with low uric acid levels ($P < .001$). Individuals with both elevated uric acid and elevated ferritin levels had significantly higher liver enzymes than individuals with either elevated uric acid or ferritin. With low uric acid and low ferritin as the reference category, individuals with high uric acid and high ferritin were significantly more likely to also have proteinuria (odds ratio, 2.66; 95% CI, 1.82–3.91).**

Conclusions: **Elevated levels of uric acid is associated with elevated ferritin levels and may serve as a risk stratification variable for presence of iron overload and hemochromatosis. (J Am Board Fam Med 2011;24:415–421.)**

Keywords: **Iron Overload, NHANES, Uric Acid**

Although iron overload and hemochromatosis have the significant clinical outcomes of cirrhosis, diabetes, and heart failure, a common but often overlooked clinical manifestation is arthritis and joint pain.[1,2] These more vague symptoms may not initially increase a clinician's suspicion of iron overload because they present for many other diseases.[3]

With no universally accepted screening recommendations for hemochromatosis or iron overload, detection in an undifferentiated patient population in primary care is difficult and may lead to detection late during the course of illness.[4,5] Although the identification of the human hemochromatosis (HFE) gene and the common mutations related to hemochromatosis suggested potential screening based on these mutations, large population-based screening studies have confirmed that disease penetrance in HFE gene–related hereditary hemochromatosis is lower than previously believed, making universal population-based screening based on genetic markers unattractive.[6] Consequently, targeted screening or case finding based on clinical features that may suggest iron overload may be a more useful strategy. Risk stratification of patients is a common strategy that guides screening among undifferentiated patient populations for diseases like diabetes and group A streptococcal pharyngitis.[7,8] Clinical markers will help to identify the patients at higher risk, thereby increasing the yield of screening.

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Elevations in uric acid may be a useful marker to cue clinicians to suspect and investigate the presence of iron overload. High uric acid has been shown to lead to gout and concomitant joint pain.[9,10] Gout is a common condition, and the diagnosed disease affects more than 4.7 million Americans aged 40 years and older.[11] The primary outcomes of acute gout are joint swelling, joint tenderness, and patient global assessment and activity limitations. When dealing with gout, the leading patient concerns are pain and mobility problems.[10] Moreover, high uric acid is associated with nonalcoholic liver disease and cardiovascular disease.[12,13]

Evidence investigating this relationship between elevated uric acid and iron overload is limited, but one study did provide findings that as ferritin increases, levels of uric acid increase as well.[14] Thus, the purpose of this study was to examine the relationship between iron overload as indicated by elevated ferritin levels and elevated uric acid levels, particularly in the context of symptoms of joint pain and mobility limitations.

Methods

The data for this study were derived from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002, a nationally representative sample of the noninstitutionalized US population. The NHANES design includes an oversampling of minorities and an ability to make population estimates. More information about the methodology of the NHANES 1999 to 2002, including laboratory assessment, can be found at the National Center for Health Statistics website.[15] This study included participants older than 20 years of age. Everyone in the study participated in the interview and the laboratory and physical examination portions of the NHANES.

Variables

Ferritin

Serum ferritin levels were available in the NHANES 1999 to 2002 for adults and was measured using the Bio-Rad Laboratories' "QuantImune Ferritin Immunoradiometric Assay" kit (Anaheim, CA), which is a single-incubation, 2-site immunoradiometric assay.[16,17] Levels of serum ferritin >200 ng/mL in women and >300 ng/mL in men were considered elevated and indicative of iron overload.[18,19]

Uric Acid

Serum uric acid also was measured in the NHANES. Uric acid was oxidized by the specific enzyme uricase to form allantoin and hydrogen peroxide. The intensity of the red color formed was proportional to the uric acid concentration. The sample was initially incubated with a reagent mixture containing ascorbate oxidase and a clearing system, eliminating any ascorbic acid in the preliminary reaction. Once the starter reagent is added, oxidation of uric acid by uricase begins. Uric acid was characterized as high (>7 mg/dL in men and >6 mg/dL in women) or low for this study. These levels correspond to a diagnosis classification for gout.[20,21]

Arthritis, Joint Pain, and Physical Functioning

We evaluated several variables included in the NHANES that were relevant to joint pain and activity limitations. Items from the questionnaire portion of the NHANES 1999 to 2002 included, Has a doctor or other health professional ever told you that you had arthritis? and, During the past 12 months, have you had pain, aching, stiffness, or swelling in or around a joint? (Do not include neck pain.) Responses to these 2 questions were "yes" or "no." Other questions included: By yourself and without using any special equipment, how much difficulty do you have…stooping, crouching, or kneeling? By yourself and without using any special equipment, how much difficulty do you have…walking from one room to another on the same level? and, By yourself and without using any special equipment, how much difficulty do you have…standing up from an armless straight chair? Responses to these 3 questions were "no difficulty," "some difficulty," "much difficulty," and "unable to do." The responses to these questions were analyzed as "no difficulty" versus "some difficulty"/"much difficulty"/"unable to do."

Liver enzyme tests

Liver function was assessed as an outcome because of the importance of cirrhosis as a manifestation of iron overload.[22] In addition, some evidence suggests that hyperuricemia is associated with elevated liver enzymes and cirrhosis.[23] The NHANES contained assays of several liver function tests aspartate

aminotransferase, alanine aminotransferase, and γ-glutamyl transaminase. More specifics regarding the method of assessment of the enzymes is contained elsewhere.[24]

Renal Function

We evaluated renal function as an outcome. Hyperuricemia has been linked to renal dysfunction.[14,25] Although there is significantly less information about iron overload and renal function, there is some evidence that excessive iron may be nephrotoxic.[26,27] The urinary albumin-to-creatinine ratio was used to classify persons as normal (<30 mg/g) or as having proteinuria (≥30 mg/g).

Control Variables

Age, sex, race/ethnicity, kidney condition, liver condition, and alcohol consumption were used as control variables in logistic regressions. Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, Mexican American, other race or multiracial, and other Hispanic. Kidney condition was determined by response to the question, Have you ever been told by a doctor or other health professional that you had weak or failing kidneys (do not include kidney stones, bladder infections, or incontinence)? Liver condition was determined by response to the question, Has a doctor or other health professional ever told you that you had any kind of liver condition? Alcohol consumption was estimated from the dietary recall portion of the NHANES in grams of alcohol.

Analysis

Because the NHANES survey is based on a complex sampling design that makes it representative of the noninstitutionalized US population, we are able to make nationally representative estimates. We used SUDAAN software (Research Triangle Institute, Research Triangle Park, NC) to account for the weighting and complex sampling design.

Initially, we computed bivariate analyses and evaluated liver enzymes; albumin-creatinine ratios; and arthritis, joint pain, and physical functioning by high versus low ferritin and by high and low uric acid. We further evaluated the combination of uric acid with arthritis, joint pain, and physical functioning to see the association with high ferritin levels in logistic regressions adjusted for age, sex, and race/ethnicity.

To examine whether the combination of high uric acid and high ferritin could have deleterious consequences, we looked at combinations of uric acid and ferritin with several outcomes. Because of the importance of cirrhosis as an outcome in iron overload and hemochromatosis, we computed multivariate statistics. Through linear regressions with conditional marginals, we evaluated the relationship between uric acid and ferritin with the liver enzymes of aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transaminase by computing means adjusted for age, sex, and race/ethnicity. We also used logistic regressions to evaluate the uric acid ferritin combinations with the outcome of renal function as indicated by the albumin:creatinine ratio. The proportion of individuals with proteinuria in each group was assessed while adjusting for age, sex, race/ethnicity, kidney condition, liver condition, and alcohol consumption.

Results

Table 1 presents the demographics of the sample; 10.9% of the sample had high ferritin and 17.6% had high uric acid. Among individuals with high

Table 1. Demographics of the Sample

Unweighted N	8,270
Weighted N	176,423,413
Ferritin	
Elevated	10.8
Normal	89.2
Uric acid	
Elevated	17.6
Normal	82.4
Joint pain	
Yes	44.8
No	55.2
Age (years)	
20–44	50.9
45–64	32.8
≥65	16.3
Sex	
Male	48.1
Female	51.9
Race/ethnicity	
Non-Hispanic white	72.6
Non-Hispanic black	10.0
Mexican American	7.0
Other Hispanic	6.9
Other race	3.4

Values presentence as percents.

Table 2. Relationships with Elevated Ferritin*

	High Ferritin	Low Ferritin	*P*
Uric acid (mean mg/dL)	6.15	5.27	<.01
ALT (mean U/L)	39.46	24.47	<.01
AST (mean U/L)	32.65	23.50	<.01
GGT (mean U/L)	55.77	27.58	<.01
Albumin-creatinine ratio ≥30 (%)	16.60	8.75	<.01
Difficulty stooping (%)	24.13	17.29	<.01
Difficulty walking (%)	5.23	3.18	.01
Difficulty standing (%)	11.74	8.08	<.01
Arthritis (%)	28.79	20.82	<.01
Joint pain (%)	47.18	44.46	.33

*High ferritin: >300 ng/mL for men, >200 ng/mL for women.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

uric acid, 20.7% had high ferritin, whereas only 8.8% of individuals with low uric acid had high ferritin ($P < .001$).

Tables 2 and 3 show that elevated ferritin is associated with elevated uric acid. The mean ferritin levels were 181.30 ng/mL for those with high uric acid and 116.90 ng/mL for those with low uric acid. For persons with high ferritin, mean uric acid was 6.12 mg/dL, whereas among persons with low ferritin the mean uric acid was 5.27 mg/dL. The Spearman correlation between serum ferritin and uric acid was 0.43 ($P < .0001$). In addition, elevated ferritin and elevated uric acid are both associated with arthritis and activity limitation, elevated liver enzymes, and proteinuria. Looking at men and women separately, 13.6% of men with high ferritin had proteinuria, whereas 8.0% of men with low ferritin had proteinuria ($P = .0015$). Among women with high ferritin, 22.8% had proteinuria whereas 9.4% of women with low ferritin had proteinuria ($P < .0001$).

The regression results presented in Table 4 indicate that elevated uric acid is significantly associated with elevated ferritin whether arthritis or activity limitation is present or not. Among persons with high uric acid, those with no joint pain had an odds ratio (OR) for elevated ferritin of 2.45 (95% CI, 1.87–3.19), and those with joint pain had an OR of 2.00 (95% CI, 1.52–2.63) for elevated ferritin. Similar results were seen for high uric acid levels and difficulty stooping, difficulty walking, and arthritis.

Table 5 shows that individuals who have both elevated uric acid and elevated ferritin have significantly higher liver enzymes than individuals with only elevated uric acid or only elevated ferritin. Similarly, with low uric acid and low ferritin as the reference category, individuals with high uric acid and high ferritin are significantly more likely to

Table 3. Relationships with Elevated Uric Acid*

	High Uric Acid	Low Uric Acid	*P*
Ferritin (mean ng/mL)	181.66	116.66	<.01
ALT (mean U/L)	34.24	24.36	<.01
AST (mean U/L)	29.16	23.49	<.01
GGT (mean U/L)	42.57	28.09	<.01
Albumin-creatinine ratio ≥30 (%)	16.47	8.14	<.01
Difficulty stooping (%)	27.49	16.02	<.01
Difficulty walking (%)	7.00	2.64	<.01
Difficulty standing (%)	15.31	7.02	<.01
Arthritis (%)	31.84	19.52	<.01
Joint pain (%)	52.04	43.21	<.01

*High uric acid: >7 mg/dL for men, >6 mg/dL for women.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

Table 4. Logistic Regressions Using Combinations of Arthritis, Joint Pain, and Physical Functioning with Uric Acid to Determine the Likelihood of Elevated Ferritin[1,2,3]

Uric Acid	Arthritis or Activity Limitation	Odds Ratio (95% CI)
Low	Stooping normal	1.00
Low	Stooping difficult	1.07 (0.84–1.38)
High	Stooping normal	2.54 (2.01–3.22)
High	Stooping difficult	1.57 (1.12–2.19)
Low	Walking normal	1.00
Low	Walking difficult	1.04 (0.65–1.67)
High	Walking normal	2.19 (1.78–2.69)
High	Walking difficult	2.26 (1.25–4.08)
Low	Standing normal	1.00
Low	Standing difficult	1.19 (0.86–1.64)
High	Standing normal	2.44 (1.97–3.03)
High	Standing difficult	1.30 (0.83–2.03)
Low	No arthritis	1.00
Low	Arthritis	1.16 (0.92–1.48)
High	No arthritis	2.50 (1.97–3.19)
High	Arthritis	1.88 (1.35–2.62)
Low	No joint pain	1.00
Low	Joint pain	1.04 (0.84–1.28)
High	No joint pain	2.48 (1.88–3.27)
High	Joint pain	2.00 (1.51–2.66)

High uric acid: >7 mg/dL for men, >6 mg/dL for women. High ferritin: >300 ng/mL for men, >200 ng/mL for women. Adjusted for age, sex, race/ethnicity, kidney condition, liver condition, and alcohol consumption.

have proteinuria also (OR, 2.66; 95% CI, 1.82–3.91). The association with proteinuria was reduced in the case of high uric acid and low ferritin (OR, 1.66; 95% CI, 1.29–2.12) or low uric acid and high ferritin (OR, 1.40; 95% CI, 1.03–1.90).

Discussion

Early detection of iron overload and hemochromatosis is very important because early treatment is effective in preventing the development of significant morbidity.[3] Universal screening is not advocated, and targeted case finding by clinical markers that increase the risk of iron overload has been suggested.[6] The findings of this study demonstrate the utility of uric acid as a marker that may guide targeted screening. This study adds new knowledge in that uric acid has not been identified previously as a risk factor for the presence of concomitant iron overload. In this nationally representative study, not only was elevated uric acid associated with the presence of iron overload, but the presence of elevated uric acid with elevated ferritin was associated with worse hepatic and renal function than with elevation of either marker alone. This suggests an even greater need to look for iron overload when patients present with elevated uric acid levels.

The importance of this finding in a clinical setting is that undiagnosed hemochromatosis should be considered as a possibility when there are elevated levels of uric acid. An elevated level of uric acid, or the presentation of gout, should cue physicians to consider the possibility of undiagnosed hemochromatosis, even if there is an absence of other related symptoms. The present data show that elevated uric acid was associated with elevated ferritin even in the absence of symptoms like joint pain or mobility limitations.

In terms of a physiologic mechanism linking elevated uric acid to elevated ferritin, the pathway currently is unclear. Uric acid is associated with inflammation, but it also functions as a strong endogenous antioxidant.[28] This has led some to contend that elevated uric acid should be protective by blocking lipid peroxidation. However, this theory is not supported by evidence that higher uric acid levels are associated with worse outcomes.[12,29] What is more likely is that the increase in serum uric acid, rather than being protective, may reflect

Table 5. Mean Liver Enzymes With Combinations of Uric Acid and Ferritin*

	Low Uric Acid		High Uric Acid	
	Low Ferritin	High Ferritin	Low Ferritin	High Ferritin
ALT (U/L)	23.7	31.6	28.8	54.9†
AST (U/L)	23.0	28.6	26.1	40.7†
GGT (U/L)	26.2	48.0	35.1	71.1†

*Adjusted for age, sex, race/ethnicity, kidney condition, liver condition, and alcohol consumption.
†Significantly different ($P < .05$) from each of the other 3 categories.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

a compensatory mechanism to counter increased oxidative stress.[30] Gout or elevated uric acid may best be seen as a risk factor and cue to suspect iron overload and target screening rather than as a physiologic pathway.

There are several limitations to this study. First, the design is cross-sectional, and thus causality cannot be determined. It is unclear whether elevated ferritin stimulates uric acid production or whether strategies to decrease uric acid or ferritin affect the other. Second, although we used clinical laboratory levels consistent with gout and iron overload, we do not know how many patients were previously diagnosed. Third, the NHANES offers estimates for the majority of individuals in the United States but is restricted to only noninstitutionalized individuals in the US. In addition, NHANES is based on several variables that are based on self-reported data from patients, like fatigue and difficulties stooping, which increases the possibility of response bias for these questions.[31] Finally, ferritin may be increased in a variety of conditions and elevated by several different factors. We accounted in our analysis for common factors like alcohol use; however, it is possible that elevated ferritin may not represent the presence of hemochromatosis or iron overload. Elevated iron markers like transferrin saturation and ferritin are the first-line screeners for hemochromatosis and iron overload. Our findings suggest that, rather than drawing the conclusion that high uric acid represents hemochromatosis, more targeted screening for iron overload may be warranted.

Conclusion

Uric acid and gout should increase a clinician's level of suspicion of the presence of iron overload. With no universal screening advocated for hemochromatosis or iron overload, targeted screening based on this marker may be worthwhile as a strategy to identify iron overload and to initiate treatment. The results shown here suggest that elevated levels of uric acid should cue clinicians to consider further tests to rule out the concomitant presence of iron overload.

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