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The Independent Impact of Congestive Heart Failure Status and Diuretic Use on Serum Uric Acid Among Men with a High Cardiovascular Risk Profile: A Prospective Longitudinal Study

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Abstract

Objective—To evaluate the independent impact of congestive heart failure (CHF) status (compensation or decompensation) on serum uric acid levels among men with high cardiovascular risk profile.

Method—We analyzed 11,681 men from the Multiple Risk Factor Interventional Trial, using data prospectively collected at baseline and annually over 6 years (64,644 visits). We evaluated the impact of change in CHF status during study follow-up, as compared with study baseline, on hyperuricemia (serum uric acid ≥ 7 mg/dL) and serum uric acid levels, using generalized estimating equations, adjusting for age, race, weight, weight change, education, alcohol intake, diuretic use, hypertension, serum creatinine level, and dietary factors. Similarly, we evaluated the independent impact of change in diuretic use (initiation or discontinuation).

Results—At baseline, mean serum uric acid was 6.88 mg/dL. Compared with no change in CHF status, odds ratios of hyperuricemia were 1.67 (95% CI, 1.21 to 2.32) for CHF decompensation and 0.21 (95% CI, 0.08 to 0.55) for compensation. The corresponding uric acid differences were 0.41 (95% CI, 0.20 to 0.62) and -1.00 (95% CI, -1.72 to -0.27), respectively. The odds ratios for initiation and discontinuation of diuretic were 3.32 (95% CI, 3.06 to 3.61) and 0.39 (95% CI, 0.35 to 0.44).

Conclusions—CHF decompensation and diuretic use are both independently associated with increased odds of hyperuricemia among men with a high cardiovascular risk profile, whereas CHF recovery and diuretic discontinuation are associated with substantially lower odds of hyperuricemia.

Keywords

congestive heart failure; diuretics; uric acid; hyperuricemia; gout

Hyperuricemia is the precursor of gout, a common and excruciatingly painful inflammatory arthritis (1,2). Conditions associated with tissue hypoxia, increased lactate levels, or accelerated consumption of adenosine triphosphate could increase the risk of hyperuricemia and gout (3), but the relevant epidemiologic data are scarce. For example, a prototypic condition associated with these pathophysiologic states is congestive heart failure (CHF) (4), but prospective data on its magnitude of association with hyperuricemia or gout are scarce. Recently, a case-control study that included only 9 patients with CHF reported a multivariate odds ratio (OR) of 40.1 with a wide confidence interval (3.6 to 437.2) for the association between CHF and gout (5). Interestingly, this study also reported that diuretic use did not increase the risk of gout after adjusting for CHF and other cardiovascular conditions. These findings call for large-scale confirmation on the independent impact of CHF as well as that of diuretic use. To address these issues, we performed longitudinal analyses using prospectively collected data from 11,681 men with a high cardiovascular risk profile in the Multiple Risk Factor Intervention Trial (MRFIT) over a 6-year follow-up period. Our primary objective was to examine the independent impact of the change of CHF status (decompensation versus compensation) from the study baseline on hyperuricemia and serum uric acid documented during the study follow-up. We also evaluated the independent impact of change in diuretic use status (use to no use versus no use to use).

METHODS

Study Population

The MRFIT was a large collaborative randomized clinical trial designed to evaluate the effect of multiple risk factor intervention on mortality rate from coronary heart disease among high-risk men. Subjects were eligible if scores for the combination of 3 risk factors (smoking, hyperlipidemia, and hypertension) were sufficiently high to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study. Detailed descriptions of the MRFIT have been published elsewhere (6-8). Briefly, between 1973 and 1976, the MRFIT investigators screened 361,662 men for eligibility at 22 different clinical centers. Of this group, 12,866 men between the ages of 35 and 57 years were randomly assigned to either a special intervention group ($n = 6428$) or a usual care group ($n = 6438$). Participants were followed for 7 years for annual visits and the follow-up rate was >90%.

Since CHF was an exclusion criterion of the MRFIT, none of the participants had a diagnosis of CHF at baseline. Because our primary interest was to assess the impact of change in CHF status in both directions (ie, compensation to decompensation versus decompensation to compensation), we defined the first annual visit of the MRFIT (ie, 1 year after the trial's original baseline) as our study baseline of the current study. The current study included 11,681 men (64,644 visits) among MRFIT participants who had the first annual visit (our study baseline), at least 1 follow-up visit the subsequent year, and had complete data from these visits for serum urate level (outcome); CHF status and diuretic use (exposure); and other covariates (ie, age, race, education level, weight, hypertension, serum creatinine level, alcohol intake, and dietary variables).

Assessment of Congestive Heart Failure Status

In the MRFIT, CHF was defined by the presence of 2 major and 2 minor criteria. The major criteria were presence of (1) paroxysmal nocturnal dyspnea; (2) distended neck veins; (3) rales with unexplained dyspnea, during the annual follow-up visit. The minor criteria were (1) bilateral ankle swelling; (2) dyspnea on exertion; (3) hepato-megaly; (4) decrease in vital capacity by 1/3 from maximum record; and (5) tachycardia, during the annual follow-up visit. CHF decompensation at each visit was defined when participants without CHF at our baseline visit developed the CHF criteria at that follow-up visit, whereas CHF compensation at each visit was defined when participants with CHF at our baseline visit had clinical improvement such that they no longer met the CHF criteria at that follow-up visit.

Assessment of Serum Uric Acid and Hyperuricemia

Serum uric acid levels and other laboratory tests, including lipid profiles, blood glucose levels, and blood chemistry tests, were performed at baseline and annually there-after (6). Blood samples were sent to a central laboratory for analysis, and the results were determined as previously described (6). Our definition of hyperuricemia was serum uric acid 7 mg/dL or above (9).

Covariates

At baseline and every subsequent year, subjects provided a detailed medical history and underwent a full physical examination, including weight measurements. Procedures for the visits, including methods for measuring weight and other covariates, have been described in detail previously (10). Diuretic use was assessed from questionnaire and updated in each annual visit. BMI was calculated as the weight in kilograms divided by the square of the height in meters. In the MRFIT, 24-hour dietary recalls were obtained at baseline and during follow-up visits (11-13). Glomerular filtration rate (GFR) was estimated by using the simplified Modification of Diet in Renal Disease study equation (14-16): $GFR (mL/min \text{ per } 1.73 \text{ m}^2) = 186 \times (\text{serum creatinine level [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times [1.212, \text{ if African American}]$. Standard and random-zero blood pressure measurements were recorded as the average of 2 measurements. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications at each visit.

Statistical Analysis

To quantify the effect of CHF status change on hyperuricemia, we performed longitudinal analysis using logistic regression models with generalized estimating equations to incorporate the correlation among repeated observations in each participant. Our multivariate model was adjusted for baseline covariates (age, race, education, weight) and time-varying covariates (weight change, alcohol intake, hypertension, diuretic use, serum creatinine level, and dietary intakes of fructose, caffeine, total protein, saturated fat, monounsaturated fat, polyunsaturated fat, and fiber). As our secondary analysis, we performed linear regression with generalized estimating equations to assess the association between change in CHF status and serum uric acid level, modeled as a continuous variable.

Similar analyses were performed to assess the impact of change in diuretic use (addition or discontinuation) on hyperuricemia and serum uric acid levels.

In a sensitivity analysis, we limited our study population to the participants whose CHF status changed over time ($n = 236$), ie, visit-based analyses but only including those 236 participants whose CHF status changed over time. To this end, we employed conditional logistic regressions for the outcome of hyperuricemia (yes or no). This approach provides estimates that are statistically equivalent to those from generalized (nonlinear) mixed models (17) and is computationally more efficient. We also performed linear mixed models for the outcome of serum uric acid level (continuous) (18). All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC). For all ORs and difference estimates, we calculated 95% confidence intervals (95% CIs). All P values were 2-sided.

RESULTS

Baseline Characteristics

The mean baseline age of the participants was 47 years. The mean serum uric acid level was 6.88 mg/dL with 44.4% of men having hyperuricemia. The baseline characteristics of the study population according to CHF status are shown in Table 1. Participants with CHF tended to be older and less educated and tended to consume less caffeine and protein.

CHF Status, Diuretic Use, and Hyperuricemia

During the 6 years of follow-up, CHF decompensation was documented in 218 visits and CHF compensation was documented in 132 visits. Compared with no change in CHF status, CHF decompensation was associated with hyperuricemia (unadjusted OR 1.62; 95% CI, 1.20 to 2.17), whereas CHF compensation was inversely associated with hyperuricemia (OR 0.35; 95% CI, 0.17 to 0.73) (Table 2). After adjusting for baseline covariates (age, race, education, weight) and time-varying covariates including weight change, hypertension, diuretic use, renal function, and alcohol intake, the magnitude of association with decompensation remained similar, whereas the inverse association with compensation became stronger (multivariate OR 0.21; 95% CI, 0.08 to 0.55). Further adjustment for time-varying dietary factors did not change the result of the multivariate model materially (Table 2). Correspondingly, CHF decompensation in the multivariable model was associated with a 0.41 mg/dL (95% CI, 0.20 to 0.62) increase in serum uric acid compared with no change in CHF status, whereas CHF compensation was associated with a 1.00 mg/dL (95% CI, -1.72 to -0.27) reduction in serum uric acid levels (Table 2).

Compared with no change in diuretic use, adding diuretic was independently associated with hyperuricemia (multivariate OR 3.32; 95% CI, 3.06 to 3.61), whereas discontinuation was inversely associated with hyperuricemia (multivariate OR 0.39; 95% CI, 0.35 to 0.44) (Table 2). Correspondingly, addition and discontinuation of diuretics were associated with 0.89 mg/dL (95% CI, 0.84 to 0.95) increase and 0.66 mg/dL (95% CI, -0.73 to -0.58) decrease in serum uric acid levels, respectively, when compared with no change in diuretic status, in the multivariable model (Table 3).

Analysis Limited to Participants with Change in CHF Status

In the analysis limited to participants whose CHF status changed over time, we found a significant improvement in the odds of hyperuricemia with compensation of CHF status (multivariate OR, 0.14; 95% CI, 0.04 to 0.47), whereas the decompensation of CHF status showed an insignificant increase in the odds of hyperuricemia (multivariate OR, 1.28; 95% CI, 0.81 to 2.00). In the linear mixed model using serum uric acid level as a continuous variable, both compensation and decompensation in CHF were significantly associated with serum uric acid level (-0.72 mg/dL, 95% CI, -1.07 to -0.36 and 0.25 mg/dL, 95% CI, 0.09 to 0.40 , respectively).

DISCUSSION

In this large prospective cohort of men with a high cardiovascular risk profile, we found that CHF decompensation was associated with 67% higher odds of hyperuricemia, whereas CHF improvement was inversely associated with 79% lower odds of hyperuricemia. Furthermore, initiation of diuretic use was associated with over 3 times higher odds of hyperuricemia and conversely discontinuation of diuretic was associated with 61% lower odds. These associations were mutually independent of each other and of other purported risk factors, such as time-varying age, weight change, hypertension, renal function, alcohol intake, and dietary factors. These results indicate that CHF status and diuretic use both substantially contribute to the risk of hyperuricemia. Furthermore, effective management of CHF and appropriate discontinuation of diuretics could lead to a meaningful decrease in the risk of hyperuricemia in men with a high cardiovascular risk profile, who often tend to have hyperuricemia and gout.

To our knowledge, only 1 previous study reported the relation between CHF and the risk of gout. In this case control study, Janssens and colleagues found a striking relative risk of gout associated with heart failure (incidence rate ratio = 21) based on a total of 9 cases of heart failure (7 with gout and 2 with controls) (5). Mutually adjusting for diuretic use, hypertension and myocardial infarction increased the risk even further (incidence rate ratio = 40). These findings were consistent with the current data, although our risk estimates are based on hyperuricemia (uric acid level of ≥ 7 mg/dL) (19-21). Our findings further extend the link to the substantial beneficial impact of CHF improvement, adding substantially to the causal argument for the association. Together, these findings suggest that CHF is a significant risk factor for hyperuricemia and its effective management could bring meaningful reduction in the risk of hyperuricemia and likely gout. However, we do acknowledge that in the present study we did not evaluate the impact of change in CHF status on gout.

CHF likely increases serum uric acid levels both by decreased renal urate excretion and by increased urate production. For example, cellular hypoxia in CHF and an early switch to anaerobic metabolism lead to increased lactate levels, particularly during exertion in patients with CHF (22). Lactate is known to decrease renal urate excretion through URAT1 (23), thus contributing to hyperuricemia. Furthermore, reduced cellular availability of oxygen also leads to increased urate production by causing net degradation of adenosine triphosphate, which in turn results in rapid accumulation of hypoxanthine and uric acid (4,24). Based on

these mechanisms, serum uric acid levels have even been proposed to be a measure of the anaerobic threshold in patients with CHF (4).

Our results on diuretic use for hyperuricemia extend the previous studies by evaluating both the impact of initiation and the discontinuation. The association between diuretic use, uric acid, and the risk of gout has been investigated in pharmacologic experiments (25), a large cohort study for incident gout (26), and a case crossover study among gout patients (27). For example, administration of diuretics (furosemide or ethacrynic acid) led to decreased excretion of uric acid in human subjects associated with volume contraction (25). A large cohort study of men found that the multivariate relative risk associated with diuretic use for incident gout was 1.77 (95% CI, 1.42 to 2.20), after adjusting for known risk factors of gout including HTN (26). Furthermore, a case-crossover study found that a multivariate OR associated with diuretic use was 3.6 (95% CI 1.4 to 9.7) for recurrent gout attacks among patients with existing gout (27). The strong positive association with initiation of diuretics and inverse association with discontinuation add substantially to the causal link with the risk of hyperuricemia and gout. It was also notable that additionally adjusting for CHF in our study did not materially alter the association with hyperuricemia.

Several strengths and potential limitations of our study deserve comment. Our analysis included a large number of longitudinal observations (64,644 visits from 11,681 men) and provided overall precise estimates based on multiple time points. Relevant time-varying covariates were prospectively collected and adjusted for in our study, including blood pressure, weight change, medication use, alcohol intake, and renal function. Nutritional data in MRFIT, including fructose for individuals, were collected on one 24-hour dietary recall per visit, which were of limited reliability (28). Thus, adjusting for these dietary variables in our multivariable analysis may not have been effective. Finally, our study was observational; thus, we cannot rule out the possibility that unmeasured factors might have contributed to the observed associations.

Men in the MRFIT were at relatively high risk of developing coronary artery disease, and thus these results are most directly generalizable to men with a similar cardiovascular risk profile. Although the demographic characteristics of our study participants (ie, men aged 35 to 57 years) reflects a population at a high risk for hyperuricemia, the generalizability of our findings to men with a different demographic profile or lower cardiovascular risk remains to be studied. Furthermore, given the influence of female hormones on the risk of hyperuricemia in women (29,30), prospective studies of female populations would be valuable, as our results may not be generalizable to women.

In conclusion, these prospective longitudinal data indicate that CHF decompensation and diuretic use are both independently associated with hyperuricemia, whereas CHF compensation and diuretic discontinuation were inversely associated. Effective management of CHF and appropriate discontinuation of diuretics could lead to a meaningful decrease in the risk of hyperuricemia in men with a high cardiovascular risk profile.

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Table 1Baseline Characteristics According to Congestive Heart Failure Status^a

Baseline Characteristics	All Participants	Congestive Heart Failure		<i>P</i> Values ^b
		Yes	No	
Number	11,681	32	11,649	—
Age, yr	47	51	47	0.002
African American, %	7	6	7	1.000 ^c
Education (>12 grade), %	64	50	64	0.108
Hypertension, %	80	84	80	0.538
Diuretic use, %	31	28	31	0.694
BMI, kg/m ²	27	28	27	0.157
Creatinine (mean), mg/dL	1.1	1.2	1.1	0.115
Alcohol (mean), servings/wk	11	10	11	0.745
Fructose (mean), g/d	20	18	20	0.508
Caffeine (mean), mg/d	418	367	418	0.446
Protein (mean), g/d	84	75	84	0.143
Saturated fat (mean), g/d	28	27	28	0.768

^aOur study baseline was a 12-month follow-up visit of the Multiple Risk Factor Interventional Trial (see text for details).^bTwo-sample *t*-test was used for continuous variables and χ^2 test was used for dichotomous variables.^cBased on Fisher's exact test.

Table 2

Odds Ratios (OR) of Hyperuricemia (≥ 7 mg/dL) and Differences in Serum Uric Acid Levels (mg/dL) According to Congestive Heart Failure (CHF) Status Change

Outcomes	CHF Status Change		
	No Change	Decompensation	Compensation
Hyperuricemia			
Number of visits	64,294	218	132
Unadjusted OR (95% CI)	1.00 (Referent)	1.62 (1.20, 2.17)	0.35 (0.17, 0.73)
Multivariate OR ^a (95% CI)	1.00 (Referent)	1.68 (1.21, 2.33)	0.20 (0.08, 0.55)
Multivariate OR ^b (95% CI)	1.00 (Referent)	1.67 (1.21, 2.32)	0.21 (0.08, 0.55)
Serum uric acid level			
Unadjusted difference (95% CI)	0 (Referent)	0.47 (0.23, 0.70)	-0.83 (-1.52, -0.14)
Multivariate difference ^a (95% CI)	0 (Referent)	0.41 (0.20, 0.62)	-1.02 (-1.75, -0.29)
Multivariate difference ^b (95% CI)	0 (Referent)	0.41 (0.20, 0.62)	-1.00 (-1.72, -0.27)

^aAdjusted for baseline covariates (race, education level, diuretic use, hypertension, and weight), and time-varying covariates (age, change of status [diuretic use, hypertension], weight change, alcohol intake, and serum creatinine level).

^bFurther adjusted for time-varying dietary factors (intakes of fructose, caffeine, total protein, saturated fat, monounsaturated fat, polyunsaturated fat, and fiber).

Table 3

Odds Ratios (OR) of Hyperuricemia (≥ 7 mg/dL) and Differences in Serum Uric Acid Levels (mg/dL) According to Diuretic Use Change

Outcomes	Diuretic Use Change		
	No Change	Addition	Discontinuation
Hyperuricemia			
Number of visits	54,308	7535	2801
Unadjusted OR (95% CI)	1.00 (Referent)	3.66 (3.39, 3.96)	0.41 (0.37, 0.46)
Multivariate OR ^a (95% CI)	1.00 (Referent)	3.40 (3.13, 3.69)	0.39 (0.35, 0.44)
Multivariate OR ^b (95% CI)	1.00 (Referent)	3.32 (3.06, 3.61)	0.39 (0.35, 0.44)
Serum uric acid level			
Unadjusted difference (95% CI)	0 (Referent)	1.01 (0.96, 1.07)	-0.67 (-0.75, -0.59)
Multivariate difference ^a (95% CI)	0 (Referent)	0.91 (0.86, 0.97)	-0.67 (-, -0.59)
Multivariate difference ^b (95% CI)	0 (Referent)	0.89 (0.84, 0.95)	-0.66 (-0.73, -0.58)

^aAdjusted for baseline covariates (race, education level, CHF, hypertension, and weight), and time-varying covariates (age, change of status [CHF, hypertension], weight change, alcohol intake, and serum creatinine level).

^bFurther adjusted for time-varying dietary factors (intakes of fructose, caffeine, total protein, saturated fat, monounsaturated fat, polyunsaturated fat, and fiber).