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ORIGINAL RESEARCH

Uric Acid as a Novel Component of Metabolic Syndrome

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Abstract

Objective: Uric continues to be explored as a novel risk factor for Metabolic Syndrome. The purpose of our study was to identify risk factors that are associated with hyperuricemia and to better understand if uric acid might serve as a useful component of metabolic syndrome.

Methods: A cross-sectional data analysis was conducted using the 2013-2018 NHANES datasets. Sample weights were assigned by NHANES researchers to each participant allowing researchers to generalize results to all non-institutionalized US civilians. The analysis included 6,432 individuals, which were representative of 94,729,059 US citizens.

Results: We demonstrated that the risk factors that had a statistically significant relationship with UA value were fasting glucose, triglycerides, systolic BP, and waist circumference. Fasting blood glucose had an inverse relationship with UA level, indicating that for every 1-point increase in fasting blood glucose, uric acid level decreased slightly. The most adjusted model reports HDL also demonstrated an inverse relationship with UA but this relationship was attenuated after controlling for potential confounders. Triglyceride level, systolic BP, and WC had direct relationships with UA level, indicating that as each risk factor increased, UA level also increased. Waist circumference had the greatest clinical significance for UA level.

Conclusions: The findings from our study suggest that metabolic syndrome risk factors do have a relationship with UA level, both in the total population and in those with metabolic syndrome. We found general trends that indicated that fasting blood glucose and HDL had negative relationships with UA level, whereas triglycerides, systolic BP, and waist circumference have positive relationships with UA. Diastolic BP did not demonstrate a relationship with UA level, and the relationship between HDL and UA was attenuated after adjustment for confounding variables. The findings suggest a need to further explore UA as a novel risk factor for metabolic syndrome.

Keywords

NHANES, Metabolic syndrome, Uric acid, Hyperuricemia, Cardiovascular disease

Introduction

Metabolic Syndrome (MetS) is a clustering of risk factors that have been reported to increase the risk for cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes and other diseases [1,2]. The clustering of risk factors includes hyperlipidemia, elevated triglycerides, abdominal obesity, elevated blood pressure, and hyperglycemia [3-5]. Though each identified component of MetS can increase the risk of disease outcomes, the clustering of multiple risk factors has been associated with increased risk of disease [6]. MetS has increased in global populations in the last two decades [7] and is attributed to approximately 15 million deaths annually [8]. Novel biomarkers for MetS are needed to gain a better understanding of the causes associated with CVD and CKD.

Uric acid (UA) is a biomarker that is associated with MetS and has been proposed as a novel biomarker in the identification of MetS [9]. Yet, study authors report UA as simply being associated with MetS but not necessarily a cause of MetS and other diseases [9,10]. UA is associated with purine degradation and is formed in the liver with some additional production by the intestines, eventually being excreted by the kidneys.

Wu, et al. [11] reported that 43 million Americans, or nearly 22%, have elevated uric acid or hyperuricemia, and the World Health Organization (WHO) has reported

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that over 1 billion people globally have hyperuricemia [6]. Hyperuricemia has garnered attention in recent publications and research funding areas [12] and has predominantly been associated with the development of gout, but more recently has been associated with hypertension, CKD, CVD, and diabetes [13]. Additionally, emerging evidence suggests that hyperuricemia may also be associated with hyperlipidemia and other cardiovascular related diseases [14].

Increased purine metabolism through ingesting large amounts of purine-rich foods with decreasing uric acid excretion is normally associated with increases in UA levels [12]. Zeng, et al. [13] reports that hyperuricemia may also be associated with dietary factors such as seafood, alcohol intake, sugar-sweetened beverages, and the intake of excess meat. Conversely, the intake of fruits and vegetables has been associated with normal levels of UA. It should be noted that equivocal evidence exists regarding dietary factors associated with hyperuricemia [13,15,16].

Hou, et al. [12] has reported four primary indicators of hyperuricemia that include obesity related indicators of body mass index (BMI), diet, alcohol consumption and lack of physical exercise. Renal function indicators such as hypertension, diabetes, and creatinine levels have also been contributed to hyperuricemia. Indictors of liver function such as fatty liver, liver damage and bone marrow values have also been associated with hyperuricemia. Additional risk factors for hyperuricemia include smoking and increased sodium in the diet [13].

Though hyperuricemia has been studied recently and has been proposed by some study authors [17-20] as a novel risk factor for MetS, additional research is needed to identify specific and modifiable risk factors that can be associated with elevated UA in both healthy and diseased populations. Research is needed in large cohort studies to identify the risk factors that predict hyperuricemia and its relationship to MetS and to inform healthcare professionals about the need to control UA levels to reduce the risk of CVD, MetS and CKD. The purpose of our study is to identify risk factors that are associated with hyperuricemia and to better understand if UA might serve as a useful component of MetS. This association, if established, could help to identify people who are at risk for early morbidity and mortality.

Materials and Methods

The United States (US) Centers for Disease Control and Prevention (CDC) continuously conducts National Health and Nutrition Examination Surveys (NHANES) that serve to collect and report health information for the US. Data from NHANES are typically published on the CDC website in 2-year cycles alongside sample design information and analytic guidelines. The sample design includes a four-stage probability sample wherein the US is divided into counties, counties are divided into census blocks, census blocks are divided into households, and individuals within each household are examined for the survey. Everyone in the sample is assigned a sample weight that is adjusted according to the individuals' unique characteristics (sex, race, SES, etc.) and allows the sample, when extrapolated, to be representative of the entire US population. The complex survey sample weighting procedures are outlined by the NHANES analytic guidelines [14,21,22]. Using this method, the statistics produced for this sample are extrapolated to be representative of the greater US population.

We analyzed three 2-year cycles of NHANES published between the years 2013-2018, totaling 29,400 subjects. We excluded individuals from our study who had received dialysis in the year prior to the study (n = 59), were pregnant (n = 190), or were outside the age range of 18 to 79 years (n = 12,585). The upper age limit was chosen because the NHANES datasets top-code age at 79 years for de-identification purposes. Of the remaining subjects, 10,111 did not have sufficient biological information for us to classify their MetS status and 23 did not have uric acid measurements. Our final sample size included 6,432 subjects, who were representative of 94,729,059 US citizens when survey sample weights were utilized. The study was determined exempt from IRB review by the sponsoring university due to the nature of the secondary data analysis.

Demographic and variable information

The CDC provides documentation for the questionnaires, examinations, and laboratory tests conducted as part of NHANES [23]. For the current analysis, subjects were considered to have a low socioeconomic status (SES) when they fell at or below the poverty line established by the US government for the given year. Subjects were considered smokers if they reported tobacco use in the 5 days prior to the study or if they reported smoking 100 or more cigarettes in their lifetime. Physical activity was determined by using time and frequency measures reported in questionnaires regarding vigorous and moderate intensity recreational physical activity. Subjects were considered physically active if they engaged in 75 or more minutes of vigorous physical activity, 150 or more minutes of moderate physical activity, or an equivalent combination of the two [24,25]. Prescription drug use information was acquired via questionnaire and classified using the International Classification of Diseases, Tenth revision (ICD-10) codes. Medication for hyperglycemia, termed "Glucose Medication" in our results, was classified using codes R73, E11, E11.2, E11.2P, E11.4, and E11.P. Medication for dyslipidaemia, termed "Cholesterol Medication" in our results, included codes E78.0, E78.0P, and E78.1. Medication for hypertension, termed "Hypertension Medication" in our results included codes I10 and I10.P. Medication for hyperuricemia, termed "Hyperuricemia

Medication" in our results included codes E79.0, M10.9, M10.9P, and M1A.

Metabolic syndrome and its accompanying risk factors were defined using the 2009 harmonized definition published by Alberti, et al. [26]. Metabolic syndrome and "metabolically unhealthy" status were classified in individuals with three or more metabolic risk factors. Risk factors were defined as: waist circumference ≥ 102 cm in males, ≥ 88 cm in females, ≥ 90 cm in Asian males, or ≥ 80 cm in Asian females, triglycerides ≥ 150 mg/dL or prescription medication for elevated triglycerides, HDL-c < 40 mg/dL in males or < 50 mg/dL in females or prescription medication for reduced HDL-c, blood pressure systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or prescription medication for hypertension, and fasting glucose ≥ 100 mg/dL or prescription medication for hyperglycemia. Hyperuricemia was defined by a uric acid level > 7.0 mg/dL in men or > 6.0 mg/dL in women. Renal function was reported as estimated glomerular filtration rate (GFR) and was calculated using the CKD-EPI equation [27].

Statistical analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data processing and statistical analyses in the present study. Variables were assessed for normality using measures of skewness and kurtosis and by visual inspection of Q-Q plots, P-P plots, and histograms. Unweighted demographic information is only reported in Table 1 as mean and standard deviation (SD) for

Table 1: Demographics of sample population.

	Unweighted Total (n = 6,432)	Weighted Total (n = 94,729,059)	Hyperuricemia (17.66%)	Normal UA (82.34%)	*p*-value
	x̄ (SD) or *M* (IQR)	x̄ (SE)	x̄ (SE)	x̄ (SE)	
Age (years)	46.91 (17.01)	46.18 (0.38)	48.97 (0.72)	45.58 (0.41)	**< 0.0001**
Uric Acid (mg/dL)	5.46 (1.44)	5.44 (0.02)	7.46 (0.04)	5.00 (0.02)	**< 0.0001**
Fasting Glucose* (mg/dL)	101 (94, 111)	107.90 (0.48)	111.66 (1.13)	107.10 (0.50)	**0.0003**
Triglycerides* (mg/dL)	92 (62, 138)	115.00 (1.69)	149.03 (4.62)	107.68 (1.59)	**< 0.0001**
HDL* (mg/dL)	51 (42, 62)	54.42 (0.37)	49.43 (0.76)	55.50 (0.36)	**< 0.0001**
LDL (mg/dL)	111.40 (35.52)	111.86 (0.72)	115.24 (1.85)	111.14 (0.70)	**0.0313**
Systolic Blood Pressure (mmHg)	123.30 (17.93)	121.57 (0.30)	126.14 (0.75)	120.59 (0.30)	**< 0.0001**
Diastolic Blood Pressure (mmHg)	70.16 (12.23)	70.44 (0.30)	72.12 (0.57)	66.78 (0.34)	**< 0.0001**
Waist Circumference (cm)	99.37 (17.16)	99.93 (0.43)	110.50 (0.918)	87.46 (0.35)	**< 0.0001**
BMI (kg/m²)	29.34 (7.21)	29.34 (0.18)	33.55 (0.37)	28.43 (0.17)	**< 0.0001**
HOMA-IR*	2.47 (1.48, 4.31)	3.83 (0.10)	5.28 (0.32)	3.51 (0.09)	**< 0.0001**
hs-CRP* (mg/L)	1.90 (0.80, 4.46)	3.75 (0.18)	5.28 (0.45)	3.42 (0.18)	**0.0003**
BUN* (mg/dL)	13 (10, 16)	13.88 (0.12)	15.73 (0.22)	13.49 (0.12)	**< 0.0001**
SCr* (mg/dL)	0.83 (0.69, 0.98)	0.86 (0.00)	0.97 (0.01)	0.84 (0.00)	**< 0.0001**
eGFR (ml/min/1.73 m²)	97.76 (22.17)	96.61 (0.50)	87.93 (0.93)	98.48 (0.51)	**< 0.0001**
ALT* (IU/L)	20 (15, 28)	24.76 (0.28)	29.93 (0.86)	23.65 (0.24)	**< 0.0001**
	n (%)	**% (SE)**	**% (SE)**	**% (SE)**	***p*-value**
Male Sex	3140 (48.82)	49.71 (0.70)	48.13 (0.79)	57.08 (2.13)	**0.0005**
Race/Ethnicity					
Mexican American	1007 (15.66)	9.43 (1.13)	7.04 (1.19)	9.94 (1.19)	
Other Hispanic	720 (11.19)	6.52 (0.80)	5.58 (0.88)	6.72 (0.86)	
NH White	2292 (35.63)	63.48 (1.99)	64.84 (2.70)	63.18 (1.93)	
					0.0063
NH Black	1334 (20.74)	11.24 (1.11)	13.32 (1.59)	10.80 (1.05)	
NH Asian	824 (12.81)	5.50 (0.53)	6.05 (0.74)	5.38 (0.55)	
Other/Multi-Racial	255 (3.96)	3.84 (0.41)	3.17 (0.76)	3.99 (0.43)	
Low SES	1307 (22.45)	15.28 (1.06)	15.19 (1.48)	15.29 (1.10)	0.9358
MetS	2792 (43.41)	40.36 (1.07)	63.60 (2.19)	35.38 (1.04)	**< 0.0001**
CKD	929 (14.44)	11.91 (0.51)	22.55 (1.47)	9.63 (0.50)	**< 0.0001**
Physically Active	2274 (69.88)	69.22 (1.09)	65.78 (2.40)	69.88 (1.32)	0.1702

Smoker	2897 (45.04)	46.34 (1.27)	53.12 (1.95)	44.88 (1.41)	**0.0005**
Glucose Medication	766 (11.91)	9.03 (0.54)	15.07 (1.30)	7.73 (0.57)	**< 0.0001**
Cholesterol Medication	1159 (18.02)	17.07 (0.68)	22.79 (1.51)	15.85 (0.68)	**< 0.0001**
Hypertension Medication	1612 (25.06)	21.80 (0.87)	37.02 (1.83)	18.53 (0.90)	**< 0.0001**
Hyperuricemia Medication	78 (1.21)	1.20 (0.19)	2.35 (0.55)	0.96 (0.22)	**0.0117**

Table 2: Linear regression controlling for known metabolic syndrome covariates for the total sample.

Total Sample		**Model 1[a]**			**Model 2[b]**			**Model 3[c]**	
Coefficient	*B*	*SE B*	*p-value*	*B*	*SE B*	*p-value*	*B*	*SE B*	*p-value*
Intercept	*3.283*	*0.237*	*< 0.0001*	*3.974*	*0.262*	*< 0.0001*	*1.799*	*0.554*	*0.003*
Fasting glucose (mg/dL)	-0.004	0.001	**< 0.0001**	-0.005	0.001	**< 0.0001**	-0.005	0.001	**< 0.0001**
Triglycerides (mg/dL)	0.001	0.000	**0.014**	0.002	0.000	**< 0.0001**	0.002	0.001	**0.007**
HDL (mg/dL)	-0.014	0.002	**< 0.0001**	-0.002	0.002	0.375	-0.002	0.003	0.534
Systolic BP (mmHg)	0.007	0.002	**< 0.0001**	0.006	0.002	**0.002**	0.008	0.002	**< 0.001**
Diastolic BP (mmHg)	-0.001	0.003	0.717	-0.006	0.003	0.074	-0.005	0.004	0.176
WC (cm)	0.024	0.002	**< 0.0001**	0.013	0.004	**0.003**	0.013	0.005	**0.012**
R^2		0.186			0.340			0.410	

Models demonstrating the influence of metabolic risk factors on uric acid (UA) level in the total sample. Beta values (B) are expressed in mg/dL of serum uric acid. [a]: Unadjusted model demonstrating the influence of each metabolic risk factor on UA levels; [b]: Model adjusted for sex, race, hs-CRP, BMI, HOMA-IR, and smoking; [c]: Model adjusted for the same variables as model 2 with the addition of physical activity, blood urea nitrogen, serum creatinine, alanine aminotransferase (ALT), and prescription medications that treat hyperuricemia

continuous variables or frequency (n) and percentage for categorical variables. Weighted data are reported for all other aspects of the study. Weighted demographic information is reported as mean and standard error (SE) for continuous variables, or percentage and SE for categorical variables. Survey weights were assigned and utilized in all statistical analyses by means of the survey procedure in the statistical analysis software. A domain statement was used to incorporate inclusion criteria, ensuring the accuracy of sample and SE values. Chi-square tests and simple regression were used to determine significant differences between groups (hyperuricemia group vs. normal UA group) when analyzing categorical and continuous data, respectively. Linear regression analyses were also conducted using sample weights. Probability values were considered significant at the 0.05 level and below.

Results

There were 6,432 study subjects included in the study after consideration of inclusion criteria. When using survey sample weights, these individuals were representative of 94,729,059 non-institutionalized US civilians, 49.71% of which were males (Table 1). The frequency of MetS in our sample was 40.36%, and the frequency of hyperuricemia was 17.66%. Of those who had hyperuricemia, the proportion of those with MetS was 63.6% compared to 35.38% in those with normal UA (p for difference < 0.0001). Additionally, those with hyperuricemia tended to be older and have a less favorable metabolic profile overall (p for all < 0.05). There were no significant differences in the frequency of those with low SES (p = 0.9358) or who were physically active (p = 0.1702) between the hyperuricemia and normal UA groups, though the physical activity variable had a high amount of missingness in the total sample (49.4%).

In the regression models representing the total sample (Table 2), we demonstrated that the risk factors that had a statistically significant relationship with UA value were fasting glucose, triglycerides, systolic BP, and waist circumference. Fasting blood glucose had an inverse relationship with UA level, indicating that for every 1-point increase in fasting blood glucose, uric acid level decreased slightly (B = -0.004, p < 0.0001 in Model 1). Subsequent models (Models 2 and 3) were adjusted for confounders. The most adjusted model (Model 3), which controlled for sex, race, HS-CRP, BMI, HOMA-IR, smoking, physical activity, BUN, serum creatinine, ALT, and hyperuricemia prescription demonstrated a similar result (B = -0.005, p < 0.0001). HDL also demonstrated an inverse relationship with UA (B = -0.014, p < 0.0001) but this relationship was attenuated after controlling for potential confounders in Models 2 and 3. Triglyceride level, systolic BP, and WC had direct relationships with UA level, indicating that as each risk factor increased, UA level also increased. These relationships were significant in all models, including the most adjusted model (B = 0.002, 0.008, and 0.013 and p = 0.007, < 0.001, and 0.012, in Model 3, respectively). Waist circumference demonstrated the largest B-value, and therefore had the greatest clinical significance for UA level. Model 3 explained a moderate-to-large amount of variance in hyperuricemia level (R^2 = 0.410, Cohen's f^2 = 0.695).

The influence of MetS risk factors on UA level was

also assessed in a subsample of individuals with MetS [26] and similar results were found as compared to the total sample. The regression models (Table 3) demonstrated that fasting blood glucose and HDL both had inverse relationships with UA level (B = -0.005 and -0.013, respectively, and p < 0.001 for all). The relationship between HDL and UA was attenuated after adjusting for confounders in Models 2 and 3 (B = -0.002, p = 0.705 in Model 3). Fasting glucose maintained a significant relationship with UA after adjustment (B = -0.006, p < 0.001 in Model 3). Triglyceride level, systolic BP, and WC had direct relationships with UA level, with the most adjusted model demonstrating B-values of 0.001, 0.008, and 0.019, respectively (p = 0.033, 0.018, and 0.045, respectively). Waist circumference was the most clinically significant risk factor. Though a smaller amount of variance was explained in the models for the MetS subsample compared to the total sample, the most adjusted model did demonstrate a moderate global effect size (R^2 = 0.350, Cohen's f^2 = 0.538).

Table 4 reports the correlations between component of MetS and uric acid in the total population and the subset of those with MetS. Most correlations were small to moderate correlations with WC representing the strongest relationship with UA in the total population (R^2 = 0.339) and subset with MetS (R^2 = 0.241).

Discussion

The purpose of the present study was to identify MetS risk factors that were related to UA level utilizing a representative US-based sample from the 2013-2018 NHANES studies. The findings from our study suggest that MetS risk factors do have a relationship with UA level, both in the total population and in those with MetS. We found general trends that indicated that fasting blood glucose and HDL had negative relationships with UA level, whereas triglycerides, systolic BP, and waist circumference have positive relationships with UA. Diastolic BP did not demonstrate a relationship with UA level, and the relationship between HDL and UA was attenuated after adjustment for confounding variables. Our study both agreed [28] and disagreed [25] with previous study findings.

Triglycerides were a significant predictor of hyperuricemias in the total sample and the subset of participants with MetS. Both triglycerides and UA are associated with insulin resistance, oxidative stress and inflammation and UA may increase triglycerides synthesis through the activation of fatty acid synthase [26]. Along with triglycerides, CRP was statistically and clinically significant between these two groups with the hyperuricemia group having a higher level of inflammation. The mechanisms underlying the

Table 3: Linear regression controlling known metabolic syndrome covariates with a subset of study participants with metabolic syndrome.

MetS Subsample		**Model 1[a]**			**Model 2[b]**			**Model 3[c]**	
Coefficient	*B*	*SE B*	*p-value*	*B*	*SE B*	*p-value*	*B*	*SE B*	*p-value*
Intercept	*3.618*	*0.485*	*< 0.0001*	*4.574*	*0.603*	*< 0.0001*	*0.334*	*0.858*	*0.700*
Fasting glucose (mg/dL)	-0.005	0.001	**< 0.0001**	-0.007	0.001	**< 0.0001**	-0.006	0.001	**< 0.001**
Triglycerides (mg/dL)	0.001	0.000	0.059	0.001	0.000	**0.001**	0.001	0.001	**0.033**
HDL (mg/dL)	-0.013	0.003	**< 0.001**	-0.004	0.003	0.194	-0.002	0.005	0.705
Systolic BP (mmHg)	0.005	0.002	**0.009**	0.006	0.002	**0.019**	0.008	0.003	**0.018**
Diastolic BP (mmHg)	-0.001	0.003	0.663	-0.005	0.004	0.174	-0.001	0.005	0.794
WC (cm)	0.024	0.003	**< 0.0001**	0.011	0.009	0.194	0.019	0.009	**0.045**
R^2		0.116			0.245			0.350	

Models demonstrating the influence of metabolic risk factors on uric acid (UA) level in the subsample with metabolic syndrome. Beta values (*B*) are expressed in mg/dL of serum uric acid. [a]: Unadjusted model demonstrating the influence of each metabolic risk factor on UA levels; [b]: Model adjusted for sex, race, hs-CRP, BMI, HOMA-IR, and smoking; [c]: Model adjusted for the same variables as model 2 with the addition of physical activity, blood urea nitrogen, serum creatinine, alanine aminotransferase (ALT), and prescription medications that treat hyperuricemia

Table 4: Correlations between known risk factors for metabolic syndrome and uric acid in the total population and those with metabolic syndrome.

	Total Group (n = 6,432)	**MetS Group**
Fasting Glucose	**r = 0.038, p = 0.002**	**r = -0.094, p < 0.0001**
Triglycerides	**r = 0.176, p < 0.0001**	**r = 0.083, p < 0.0001**
HDL	**r = -0.278, p < 0.0001**	**r = -0.194, p < 0.0001**
Systolic BP	**r = 0.164, p < 0.0001**	r = 0.011, p = 0.555
Diastolic BP	**r = 0.105, p < 0.0001**	r = 0.021, p = 0.273
Waist Circumference	**r = 0.339, p < 0.0001**	**r = 0.241, p < 0.0001**

association between hyperuricemia an inflammation is not yet fully understood, however several findings have been reported [29-31]. First, UA has been reported to have pro-inflammatory effects at elevated levels [32]. Additionally, oxidation of UA through reactive oxidative species (ROS) can cause oxidative damage to tissues and cells associated with the release of pro-inflammatory cytokines. It should be noted that the hyperuricemia group had a statistically significant higher level of triglycerides suggesting that a relationship does exist with UA and could be related to higher levels of inflammation.

HDL, though a component of MetS, was not a significant predictor of UA in our study when other biomarkers for CVD were controlled. HDL was a significant inverse predictor in the first model of the study populations but was attenuated when controlling for known risk factors of MetS. Recent study authors [33] have reported that hyperuricemia is associated with changes in lipid metabolism, specifically with an increase in LDL and a decrease in HDL cholesterol. UA has been reported to be associated with an increase in the production of LDL in human liver cells causing an increased risk for CVD. HDL in both the normal and hyperuricemic groups were above minimum thresholds demonstrating lower risk in each group, suggesting that triglycerides may play a more significant role in UA levels than HDL. Our study partially agreed with the findings [5] that triglycerides were a persistent predictor of hyperuricemia across all models but HDL was not predictive when other confounders were added to the model. It is possible that lipids may not have direct effect on UA [5,33], yet, confounders that were controlled for in our study may suggest lipids, specifically HDL and LDL may not be a strong predictor, only triglycerides. These findings need further exploration.

Fasting glucose was a significant predictor of hyperuricemia in our study in both the total sample and a subset of participants who met the criteria for MetS. Fasting glucose and UA in our study had an inverse relationship with each 1 mg/dL increase in glucose associated with a decrease in UA levels. Studies have investigated the relationship between fasting glucose and UA with equivocal findings [2,34]. A systemic review and meta-analysis of 11 studies by Kodama, et al. [35] concluded that though individual studies reported positive correlations between fasting glucose and UA, the meta-analysis did not support a relationship. Conversely, a meta-analysis by Wang, et al. [36] reported that elevated UA levels were significantly associated with fasting glucose. The analysis included 57 studies with over 500,000 participants. Equivocal findings in previous studies could be related to other confounders related to MetS such as age, sex, and WC. Yet, our study suggests that when controlling for known risk factors for MetS, fasting glucose was a significant predictor of hyperuricemia, yet had an inverse relationship.

In our study, systolic blood pressure, but not diastolic blood pressure, was a significant predictor of hyperuricemia in the total population and the subset with MetS. Though the differences in SBP between the UA groups were not clinically significant. Previous study authors [37,38] reported significant associations between SBP and UA. Hyperuricemia may cause endothelial dysfunction and oxidative stress which can cause reduced blood vessel elasticity and increase stenosis, which can also be associated with elevated levels of SBP. Of note is that DBP was not associated with hyperuricemia in our study, which has been reported in previous literature [39].

Finally, WC was a significant predictor of UA that persisted in both the total study population and the subset of those with MetS in all regression models and was the most clinically significant predictor of UA levels. WC is a simple and reliable anthropometric measure that is commonly used as an indicator for central obesity. Central obesity has been associated with increased insulin resistance and oxidative stress all of which have been reported to be associated with elevated levels of UA [5]. Our study supports these findings as there were clinically and statistically significant differences in WC, with those that have hyperuricemia in our study having a larger WC.

Our study findings have agreed with previous literature regarding the relationship between components of MetS and UA except for HDL which was not a significant predictor of hyperuricemia in the most sophisticated regression models. Future research should further explore the relationship between UA and HDL. Future longitudinal research is needed to discover if UA in healthy populations can predict a cascade of events leading to the development of MetS. Our study suggests UA may be an important addition to components of MetS for risk prediction. The correlations revealed a small portion of variance explained, which can suggest that UA adds a novel risk factor that could be included in the components of MetS.

Several shortcomings existed in our study. Data was collected through NHANES at single time points and was cross-sectional limiting the ability to make causal inferences. Some data in NHANES is self-reported which is subject to under and overreporting of certain variables. The large sample and the sample weighting technique help overcome these shortcomings making findings from the study of importance while yielding generalizable results. A sample of those with MetS and without in our study helps lead to important findings regarding UA and components of MetS.

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