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Elevated serum uric acid is associated with peripheral endothelial dysfunction in women

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HIGHLIGHTS

- Serum uric acid is associated with microvascular peripheral endothelial dysfunction.
- Uric acid threshold for vascular health is lower than the upper normal range limit.
- Uric acid is associated with vascular health in apparently low risk individuals.

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ABSTRACT

Background and aims: Both elevated serum uric acid (SUA) and peripheral endothelial dysfunction (PED) are associated independently with cardiovascular disease (CVD). However, the association between SUA and PED is yet to be established. We hypothesized that high normal range of SUA is associated with PED.
Methods: We performed a retrospective cross-sectional analysis of patients who were referred to Mayo Clinic between 2006 and 2014 for routine cardiovascular evaluation and who underwent evaluation of Reactive Hyperemia Peripheral Arterial Tonometry (index < 2 consistent with PED). A high UA was defined as ≥5 mg/dL, in keeping with previous studies evaluating the link between SUA and CVD outcomes.
Results: One hundred forty patients were included (mean age 50.7 ± 12.9 years, 86 (61.4%) female). Twenty four patients (17.1%) had pre-existing CVD (8 (9.3%) in females). Thirty patients (21.6%) had a Framingham score > 10% (8 (9.4%) in females). Fifty eight (41.4%) had PED and 77 (55.0%) had an elevated SUA. SUA levels were higher in patients with PED compared to those without (5.5 ± 1.4 vs 4.8 ± 1.2 mg/dL; $p = 0.004$). In an univariate analysis, elevated SUA levels were associated with PED (Odds Ratio (OR): 2.7; 95% confidence interval [CI] 1.33–5.48; $p = 0.005$). In a multivariate analysis adjusting for age, sex, presence of obstructive CVD and Framingham score > 10, elevated SUA levels were associated with PED (OR 2.45; 95% CI 1.08–5.52; $p = 0.031$). After stratifying by sex, this association persisted in females only.
Conclusions: High normal SUA levels are associated with PED in women who are otherwise at low risk for CVD. Thus, SUA is a promising circulating biomarker that could be used to assist in risk stratification in female patients with chest pain and/or those undergoing evaluation of CVD risk.

1. Introduction

Elevated serum uric acid (SUA) has been associated with hypertension [1], metabolic syndrome [2] and cardiovascular disease (CVD) [3–5]. Whether an elevated SUA causes CVD *per se* or is in fact a marker of risk [6,7] it is not yet clear.

Endothelial dysfunction is often described as the first step in the atherosclerotic process and is independently associated with adverse

Abbreviations: SUA, serum uric acid; PED, peripheral endothelial dysfunction; RH-PAT, Reactive Hyperemia Peripheral Arterial Tonometry; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FMD, flow-mediated vasodilatation; HBA1C, glycated hemoglobin; T. cholesterol, total cholesterol

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cardiovascular events [8]. Impaired endothelium-mediated vasodilation is a systemic abnormality occurring in both the peripheral and coronary circulation [9]. Peripheral endothelial function can be assessed non-invasively by measuring Reactive Hyperemia Peripheral Arterial Tonometry (RH-PAT) using EndoPAT [10–12] which focusses specifically on the peripheral microvasculature. A correlation between peripheral endothelial dysfunction (PED) and coronary endothelial dysfunction (assessed using pharmacologic provocation during coronary angiography) has been demonstrated, and thus, EndoPAT can serve as a validated noninvasive surrogate for invasive coronary endothelial function measurements obtained during angiography [13]. Observational data demonstrates that individuals with minimal traditional cardiovascular risk factors who have PED have a higher incidence of cardiovascular events, including mortality, compared to those with normal peripheral endothelial function [8,14,15]. Thus, PED appears to provide prognostic information above and beyond that provided by conventional CVD risk factors.

Previous studies have demonstrated dependence of the RH-PAT index on nitric oxide, suggesting that RH-PAT scores indeed reflect changes in nitric oxide–dependent endothelial function, rather than neurohormonal activation [16]. It has been suggested that uric acid taken up by endothelial cells through uric acid transporters mediates inflammation, oxidative stress, and dephosphorylation of endothelial nitric oxide synthase, leading to endothelial dysfunction through decreased nitric oxide bioavailability [17–20]. Indeed, the association between elevated SUA and endothelial dysfunction, both peripheral and coronary, has been shown in post-menopausal women [21,22], as well as in individuals with conventional cardiovascular risk factors [23]. In addition, the definition of a pathologically elevated SUA as it pertains to non-arthritic crystal deposition, including in its role as a risk factor for CVD, is unclear, but presumed to be less than the established threshold for soft tissue and joint urate crystal deposition [24,25].

While elevated SUA has been linked to coronary endothelial dysfunction, cardiovascular risk factors and cardiovascular disease, its association with peripheral microvascular endothelial function has yet to be established. We aimed to evaluate the association of elevated SUA and PED in subjects referred evaluation of chest pain and/or cardiovascular risk. We hypothesized that there is association between PED and elevated SUA even in the high normal range.

2. Patients and methods

In the current retrospective cross-sectional study, patients were referred by their primary physicians for assessment of chest pain and/or cardiovascular risk. Patients underwent testing for PED using EndoPAT to determine RH-PAT. The decision to undertake testing for PED using EndoPAT was at the clinical discretion of the evaluating physician. Only the first test for each patient was included in the final data analysis and thus 44 tests were excluded for retesting in the same patient. The PED studies were performed in a designated quiet, temperature controlled and uniformly lit room, as previously described [26,27]. Subjects were instructed to fast for 4 h before the study and abstain from coffee or tobacco on the day of the examination. All vasoactive medications were discontinued for 24 h prior to testing. A fitted blood pressure cuff was placed on one arm, and the finger cuffs of the Endo-PAT 2000 device (Itamar Medical Inc. Ltd., Caesarea, Israel) were placed on the middle finger of each hand [28]. The EndoPAT 2000 is a Food and Drug Administration–approved noninvasive device, allows continuous recording of the signal, and interpretation is operator-independent. A fall in the arterial blood volume in the distal fingertip causes a decrease in pulsatile arterial column changes, reflected as a decrease in the measured PAT signal, and vice versa.

The reactive hyperemia protocol includes a 5-min baseline measurement, after which a blood pressure cuff on the test arm is inflated to 60 mmHg above baseline systolic blood pressure, or at least 200 mmHg for 5 min after which the cuff is deflated, and the post-deflation PAT tracing is recorded for six additional minutes. The ratio of the PAT signal after cuff release to baseline is calculated through a computer algorithm automatically normalizing for baseline signal, and indexed to the contralateral arm. Previous studies have demonstrated that a 1-min RH-PAT index of less than 2.0 correlates best with PED, with a specificity of over 96% [29].

Several studies have shown a good association between microvascular PED assessed using EndoPAT and more widely accepted methods of testing endothelial function, such as intra-arterial acetylcholine infusion and brachial artery Doppler ultrasound following reactive hyperemia [30–32].

Patients who had SUA drawn within 2 months of the PED assessment were included in the study. Patients who were on medications to lower SUA levels were excluded.

2.1. Patients' consent

The study was approved by Mayo Clinic International Review Board with compliance with the Declaration of Helsinki, and all patients provided written informed consent to participate in the protocol and have their clinical information and data used for this and other research studies.

2.2. Patients' information

Data was collected on the following parameters: demographic factors (sex and age), body mass index (BMI), presence of obstructive CVD (defined as history of percutaneous coronary intervention or coronary artery bypass graft surgery, coronary artery stenosis of ≥50% of at least one coronary artery on coronary angiogram or coronary computed tomography angiography, history of ischemic stroke or transient ischemic attack assumed not to be secondary to atrial fibrillation, carotid artery stenosis ≥50% based on Doppler ultrasound scan or computed tomography, or a clinical diagnosis of peripheral artery disease), traditional CVD risk factors (smoking status; obesity (BMI ≥ 30 kg/m^2); dyslipidemia, defined as a diagnosis of hyperlipidemia, treatment with lipid lowering therapy, low-density lipoprotein (LDL) cholesterol above target (100 mg/dL for diabetics and > 70 mg/dL for CVD patients) [33], high-density lipoprotein (HDL) cholesterol < 40 mg/dL in men or < 50 mg/dL in women, or triglycerides ≥ 150 mg/dL; type2 diabetes mellitus, defined as a known history of or treated type2 diabetes; and hypertension, defined as a known history of or treated hypertension), and presence of chronic kidney disease stage III or worse (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 based on MDRD equation34).

Data on laboratory information was also collected on the following: SUA, fasting plasma glucose (FPG), hemoglobin A1C, lipid profile, and creatinine.

2.3. Statistical analysis

We divided the study sample into those with PED (RH-PAT index < 2) versus those without PED, and compared SUA, as a continuous variable, between both groups and also compared the percentage of individuals with a SUA ≥ 5 mg/dL in each group. We elected to use a threshold of 5 mg/dL because other studies had found significant associations between SUA and PED at thresholds of 4.035, 5.236 or 6.037 mg/dL, and the median SUA for our population was 5.1 mg/dL. In addition, we undertook additional univariate analyses after stratifying by sex, age, presence of obstructive CVD and Framingham based risk for CVD. Multivariate analyses assessing the association between an elevated SUA and an abnormal RH-PAT index were performed after adjustment for sex, age, presence of obstructive CVD and Framingham based risk with further stratification by sex using the same variables except sex.

Continuous variables are presented as a mean (standard deviation)

Table 1
Patient characteristics.

Characteristic	All the subjects (N = 140)	Women (N = 86)	Men (N = 54)	*p* value[a]	Without PED (N = 82)	With PED (N = 58)	*p* value[b]
Age - mean ± SD (yr)	50.7 ± 12.9	49.9 ± 13.2	52.1 ± 12.3	0.301	51.6 ± 13.9	49.5 ± 11.5	0.330
Male sex - no./total no. (%)	54/140 (38.6)				26/82 (31.7)	28/58 (48.3)	**0.047**
Body mass index[c] - mean ± SD	28.1 ± 6.5	27.7 ± 7.2	28.7 ± 5.2	0.369	26.5 ± 5.8	30.4 ± 6.8	**< 0.001**
Obstructive CVD - no./total no. (%)	24/140 (17.1)	8/86 (9.3)	16/54 (29.6)	**0.002**	14/82 (17.1)	10/58 (17.2)	0.979
Smoking (past or current) - no./total no. (%)	52/140 (37.1)	28/86 (32.6)	24/54 (44.4)	0.157	27/82 (32.9)	25/58 (43.1)	0.22
Obesity (BMI≥30 kg/m^2) - no./total no. (%)	47/140 (33.6)	27/86 (31.4)	20/54 (37.0)	0.491	19/82 (23.2)	28/58 (48.3)	**0.002**
Dyslipidemia - no./total no. (%)	99/140 (70.7)	52/86 (60.5)	47/54 (87.0)	**< 0.001**	53/82 (64.6)	46/58 (79.3)	0.06
Type 2 diabetes - no./total no. (%)	9/140 (6.4)	2/86 (2.3)	7/54 (13.0)	**0.013**	3/82 (3.7)	6/58 (10.3)	0.112
Hypertension - no./total no. (%)	60/140 (42.9)	36/86 (41.9)	24/54 (44.4)	0.764	38/82 (46.3)	22/58 (37.9)	0.322
Framingham score > 10% - no./total no. (%)	30/139 (21.6)	8/85 (9.4)	22/54 (40.7)	**< 0.001**	16/81 (19.8)	14/58 (24.1)	0.536
Chronic kidney disease - no./total no. (%)	18/136 (13.2)	10/83 (12.0)	8/53 (15.1)	0.609	11/78 (14.1)	7/58 (12.1)	0.729
Lab data- no./total no. (%), mean ± SD							
Uric acid (mg/dL)	140/140 (100), 5.09 ± 1.34	86/86 (100), 4.50 ± 1.10	54/54 (100), 6.03 ± 1.12	**< 0.001**	82/82 (100), 4.81 ± 1.23	58/58 (100), 5.48 ± 1.39	**0.004**
FPG (mg/dL)	138/140 (98.6), 97.4 ± 17.6	84/86 (97.7), 95.5 ± 16.8	54/54 (100), 100.4 ± 18.5	0.115	81/82 (98.8), 97.0 ± 18.3	57/58 (98.3), 98.1 ± 16.7	0.701
HBA1C (%)	51/140 (36.4), 5.6 ± 0.92	27/86 (31.4), 5.4 ± 0.7	24/54 (44.4), 5.8 ± 1.1	0.072	24/82 (29.3), 5.6 ± 0.9	27/58 (46.6), 5.6 ± 1.0	0.983
T. cholesterol (mg/dL)	138/140 (98.6), 192.7 ± 47.1	84/86 (97.7), 198.0 ± 41.8	54/54 (100), 184.5 ± 53.7	0.122	80/82 (97.6), 196.1 ± 48.6	58/58 (100), 188.0 ± 45.0	0.317
LDL-C (mg/dL)	133/140 (95.0)	84/86 (97.7), 108.4 ± 34.9	49/54 (90.7), 102.1 ± 39.8	0.362	77/82 (93.9), 107.3 ± 36.5	56/58 (96.6), 104.5 ± 37.3	0.668
HDL-C (mg/dL)	138/140 (98.6), 60.7 ± 19.5	84/86 (97.7). 67.8 ± 19.5	54/54 (100), 49.6 ± 13.4	**< 0.001**	80/82 (97.6), 63.8 ± 19.9	58/58 (100), 56.4 ± 18.2	**0.026**
Non HDL-C (mg/dL)	138/140 (98.6), 132.0 ± 46.5	84/86 (97.7), 130.1 ± 38.7	54/54 (100), 134.9 ± 56.9	0.59	80/82 (97.6), 132.3 ± 46.8	58/58 (100), 131.6 ± 46.5	0.928
Triglycerides (mg/dL)	138/140 (98.6), 137.6 ± 137.6	84/86 (97.7), 108.1 ± 58.2	54/54 (100), 183.4 ± 200.3	**0.009**	80/82 (97.6), 130.4 ± 133.7	58/58 (100), 147.4 ± 143.4	0.480
eGFR (mL/min/1.73 m^2)	136/140 (97.1), 76.7 ± 19.2	83/86 (96.5), 75.6 ± 20.1	53/54 (98.1), 78.5 ± 17.7	0.388	78/82 (95.1), 73.6 ± 19.8	58/58 (100), 81.0 ± 17.5	**0.023**

PED - peripheral endothelial dysfunction, SD - Standard deviation, CVD - Cardiovascular disease, FPG - Fasting plasma glucose HBA1C- glycated hemoglobin, T. cholesterol – Total cholesterol, LDL-C - low density lipoprotein cholesterol, HDL-C - High density lipoprotein cholesterol, eGFR-estimated glomerular filtration rate (based on MDRD equation [34]).

[a] *p* value for comparing men *vs* women.

[b] *p* value for comparing those with *vs* those without PED.

[c] The body-mass index is the weight in kilograms divided by the square of the height in meters.

where data is normally distributed. Categorical variables are presented as frequencies (percentages). Differences between groups were analyzed using Student's T test for continuous variables and chi-squared test for proportions. A logistic regression model was analyzed to estimate the associations between SUA and RH-PAT index. P-values of less than 0.05 were accepted as significant. All statistical analyses were performed using JMP 9 software (SAS Institute, Inc., Cary, NC, USA).

3. Results

Testing for PED using EndoPAT was performed 722 times between January 17, 2006 and February 14, 2014 in subjects referred to Mayo Clinic for evaluation of chest pain and/or cardiovascular risk. SUA was not routinely measured as a part of cardiovascular risk assessment. Therefore, only 143 patients had SUA levels measured within 2 months of the EndoPAT test. We excluded 3 patients treated with SUA lowering medications, leaving a total of 140 patients in the analysis. Patients' baseline characteristics are summarized in Table 1. The mean age of the sample was 50.7 ± 12.9 years, and 54 (38.6%) were male. Twenty four subjects (17.1%) had obstructive CVD and 30 (21.6%) subjects had a Framingham score > 10. Women had a lower frequency of obstructive CVD, dyslipidemia, type2 diabetes and a lower Framingham score compared to men. In addition, women had lower levels of triglycerides and higher levels of HDL compared to men. SUA levels were also higher in women compared to men.

Patients with PED had a higher BMI, higher percentage of obesity, and lower level of HDL compared to patients without PED. eGFR was higher in patients with PED compared to patients without PED, although there was no difference in the percentage of patients with chronic kidney disease stage III or worse (eGFR < 60 mL/min/1.73 m^2) between the groups.

Mean SUA levels were higher in patients with PED compared to patients without PED. Among 58 patients with PED, 40 (69.0%) had UA ≥ 5 mg/dL compared to 37 patients (45.0%) out of 82 patients without PED, $p = 0.0052$.

In a univariate analysis, elevated SUA (≥5 mg/dL) was associated with PED with an odds ratio (OR) of 2.7, 95% confidence interval (CI), 1.33–5.48; $p = 0.005$, Table 2. In further univariate analyses, and after stratifying individually by sex, age, presence of obstructive CVD and Framingham score based risk (score > 10), there was a significant association between elevated SUA levels and PED in women, subjects younger than 50 years, subjects without obstructive CVD, and subjects with a Framingham score of less than 10.

In multivariate analyses (Fig. 1) adjusting for age, sex, presence of obstructive CVD and Framingham based risk, elevated SUA remained associated with PED (OR 2.45; $p = 0.031$). After stratification by sex, with adjustment for the same variables with the exception of sex, elevated SUA levels were significantly associated with PED among women only (OR 2.69; 95%CI, 1.01–7.19; $p = 0.048$).

4. Discussion

The current study demonstrates a significant association between levels of SUA in the high-normal range, ≥5 mg/dL, and PED. In univariate analyses, this significant association persisted in low risk groups including females, adults aged < 50 years, those without obstructive CVD, and those with a Framingham risk of less than 10. Finally, after adjusting for covariables, an elevated SUA was significantly associated with PED among women. Of note, women in this study had a lower frequency of obstructive CVD, dyslipidemia, type 2 diabetes, and a lower Framingham score, as well as higher levels of HDL and lower levels of triglycerides compared to men. Thus the current study contributes to the existing body of literature that underscores the potential role of SUA in identifying individuals that may be considered to be at relatively low cardiovascular risk, yet have with impaired vascular health, and therefore are at an increased risk of CVD, particularly in women.

4.1. The mechanism linking elevated UA to PED

It has been suggested that elevated SUA levels may mediate endothelial dysfunction through decreased nitric oxide bioavailability [17–20]. Previous studies have confirmed that systemic microvascular endothelial function assessed by RH-PAT scores indeed reflect changes in nitric oxide–dependent endothelial function, rather than neurohormonal activation [16]. Thus, a potential mechanism linking SUA to PED may relate to reduced activity of the nitric oxide synthase pathway. Impaired endothelium-mediated vasodilation is a generalized abnormality occurring in both the peripheral and coronary circulation [9], and a good correlation between PED and coronary endothelial dysfunction has been demonstrated [13]. Thus, the association between elevated SUA with PED in the current study could reflect systemic endothelial dysfunction and, as a consequence, potentially a higher CVD risk in these individuals, particularly given that individuals with minimal traditional cardiovascular risk factors who have PED have a higher incidence of cardiovascular events compared to those with normal peripheral endothelial function [8,16,17].

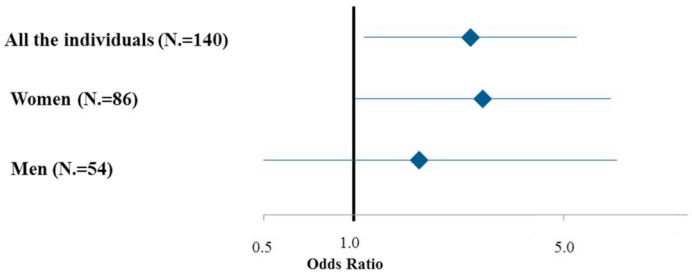
4.2. The definition of hyperuricemia appropriate to PED

The definition of hyperuricemia pertaining to non-arthritic crystal deposition, such as CVD risk, is uncertain. Saito et al. showed an

Table 2
The association between elevated serum uric acid (≥5 mg/dL) and PED.

Stratified by		No. with elevated SUA/all (%)	No. with PED/all (%)	Odds ratio (95% confidence interval)	*p* value
All Subjects		77/140 (55.0)	58/140 (41.4)	2.70 (1.33–5.48)	0.005
Gender					
	Women	32/86 (37.2)	30/86 (34.9)	**2.86 (1.14–7.19)**	**0.024**
	Men	45/54 (83.3)	28/54 (51.9)	1.43 (0.34–6.03)	0.626
Age					
	≤50 yr.	39/70 (55.7)	32/70 (45.7)	2.72 (1.02–7.27)	**0.044**
	> 50 yr.	38/70 (54.3)	26/70 (37.1)	2.70 (0.97–7.51)	0.054
Obstructive CVD					
	(−)	63/116 (54.3)	48/116 (41.4)	2.39 (1.11–5.14)	**0.025**
	(+)	14/24 (58.3)	10/24 (41.7)	5.33 (0.82–34.83)	0.069
Framingham score > 10					
	(−)	50/109 (45.9)	44/109 (40.4)	2.47 (1.13–5.41)	**0.023**
	(+)	27/30 (90.0)	14/30 (46.7)	[a]	0.088

SUA – Serum uric acid, PED - Peripheral endothelial dysfunction, CVD – Cardiovascular disease.
[a] Odds ratio could not be calculated due to no patients with SUA < 5 mg/dL and PED in the Framingham > 10 group.



	OR; (95% CI)	*p* value
All the individuals (N.=140)	2.45; (1.08-5.52)	**0.031**
Women (N.=86)	2.69; (1.01-7.19)	**0.048**
Men (N.=54)	1.65; (0.36-7.54)	0.515

Fig. 1. Odds ratio (OR) with 95% confidence interval (CI) for the association between elevated serum uric acid (≥5 mg/dL) and peripheral endothelial dysfunction based on multivariate analysis adjusting for: age, sex, presence of obstructive cardiovascular disease and Framingham based risk (> 10 or ≤10) in all the study individuals and with stratification to women and men adjusted for the same variables except sex.

association between reduced systemic endothelial function and SUA levels > 5.2 mg/dL in patients with acute coronary syndrome [36]. In subjects treated for hypertension, the association between PED assessed by flow-mediated vasodilatation (FMD) and elevated SUA levels was significant in women only with an SUA level ≥237.92 μmol/L (4.0 mg/dL) [35]. In another study, SUA ≥6.0 mg/dL was significantly associated with impaired peripheral endothelial function recovery, assessed using EndoPAT, after minor to moderate surgery [37]. Maruhashi et al. [21] found that in postmenopausal but not in premenopausal women, FMD gradually decreased in accordance with increasing SUA levels in steps ranging from < 4 mg/dL, 4 to < 5 mg/dL, 5 to < 6 mg/dL, to ≥6 mg/dL. In the current study, we extend these previous observations by demonstrating a significant association between PED and SUA at level greater than or equal to 5 mg/dL. The common finding in all of these studies, including the current study, is the significant association between elevated SUA levels and PED in a "high-normal" range of SUA, which is lower than thresholds established to define an increased risk for crystal soft tissue and/or joint deposition. It may be speculated that, similar to C-reactive protein, SUA may have a different normal range in rheumatologic disease compared to vascular disease. More studies are required to clarify the most useful and clinically relevant threshold for impaired vacular health and increased CVD risk.

4.3. Elevated SUA in low risk patients

The current study demonstrates a significant association between elevated SUA levels and PED in seemingly low risk patients. Similarly, Otani et al. [38] did not find an association between SUA and PED in either hypertensive patients, nor in other high-risk groups, but did find a significant association between SUA and PED in low risk individuals (e.g., hypertensive patients without established cardiovascular or cerebrovascular disease, chronic kidney disease, and/or diabetes). Further, the association between SUA levels and PED assessed by FMD was evaluated in Japanese men [39] without CVD who were not on any medication for cardiovascular risk management, who were divided into two groups depending on the presence of metabolic syndrome. The authors found a significant association between PED and mild hyperuricemia in patients without metabolic syndrome, while a similar association was found only with severe hyperuricemia in patients with metabolic syndrome. Conversely, in a review of the literature, Baker et al. [40] found that amongst 11 studies evaluating the role of a high SUA level as an independent risk factor for CVD events in high risk patients, 10 were supportive of an independent association, while in 10 studies evaluating healthy individuals, only 6 were supportive of an independent association. However, Baker el al.'s review focused on cardiovascular outcomes and did not include studies evaluating the association between SUA and PED as an early sign of impaired vascular health in apparently healthy or low risk subjects. Nevertheless, other studies have also demonstrated a significant association between elevated SUA levels and PED in high risk patients including patients with acute coronary syndrome [41], and patients with non-diabetic chronic kidney disease [42]. Thus, the relative association between SUA and PED in low and high risk cohorts needs further clarification. From a clinical practice standpoint, however, the significant association between SUA levels and PED in low risk patients as shown in the current study could have important clinical implications by underscoring the potential utility of SUA as an early biomarker of impaired vascular health in these low risk patients, particularly women. This in turn could help identify individuals who may benefit from earlier initiation and/or intensification of CVD risk factor management.

4.4. Is the association between SUA and PED sex-related?

The current study showed that after univariate and multivariate analyses stratifying by sex, the association between elevated SUA and PED remains significant only in women. Prasad et al. [22] found SUA levels to be significantly associated with coronary microvascular dysfunction in postmenopausal women without obstructive coronary artery disease; that study however did not include men. In another study that included both sexes, the association between PED assessed by FMD and elevated SUA levels in subjects treated for hypertension was significant in women only [35].

The association between UA and cardiovascular outcomes has also been investigated in men and women in the Chicago Heart Association Detection Project [43], and The Honolulu Heart study [44]. Each study found an independent relationship between SUA and cardiovascular outcomes in all patients. Conversely, the First National Health and Nutrition Examination Survey (NHANES I) study [45], which also included both men and women, found an independent relationship in women only.

In the current study, we also showed a significant association between elevated SUA levels and PED in women only, contributing to the body of evidence that suggests sex-based differences in this relationship. The underlying cause could be related to hormonal differences unique to each sex, but has not been delineated in the literature and requires further study. Alternatively, women tend to have lower SUA levels compared to men (by 0.5–1.0 mg/dL) [46]; however, the mean SUA level in the current study was higher in women compared to men. In addition, the women in the current study had a lower frequency of obstructive CVD and a lower Framingham score compared to men. Given the previously alluded to possible association between SUA levels and PED in low risk patients only, it may be that the association between elevated SUA levels and PED in women is in fact a reflection of the fact that the women included in the current study were of low risk, and that perhaps there is no role for sex, *per se*, in this association. More large, prospective studies are needed including both men and women with different levels of risk for CVD are required to better answer these questions.

4.5. Importance and limitations of the study

The current study demonstrates a significant association between elevated SUA levels and early signs of impaired vascular health, namely PED, in women at low risk of CVD. However, the current study has some limitations: (1) this was a retrospective cross-sectional analysis which makes deriving causal associations not possible; (2) men and

women were not homogenous with regards to the presence of CVD risk factors, which makes deriving conclusions about the interaction sex may have on the relationship between SUA and PED uncertain; (3) the use of EndoPAT testing to evaluate PED was at the discretion of the evaluating physician; (4) the prognostic value of patients with an elevated SUA and PED was not evaluated.

4.6. Conclusions

Elevated SUA, even in the high-normal range, is associated with PED in women at low risk for CVD. These findings support the use of SUA as an attractive biomarker to investigate early signs of impaired vascular health and PED in low risk patients. SUA could be used to identify individuals at an increased risk for CVD, allowing for the prompt initiation and/or intensification of risk preventative strategies.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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