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Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women

Megha Prasad, MD[1], **Eric L. Matteson, MD, MPH**[2], **Joerg Herrmann, MD**[1], **Rajiv Gulati, MD PhD**, **Charanjit S. Rihal, MD MBA**[1], **Lilach O. Lerman, MD PhD**[1], and **Amir Lerman, MD**[1]

[1]Mayo Clinic, Division of Cardiovascular Diseases, Rochester, MN

[2]Mayo Clinic, Division of Rheumatology, Rochester, MN

Abstract

Uric acid is a risk factor for coronary artery disease (CAD) in postmenopausal women but the association with inflammation and coronary microvascular endothelial dysfunction (CED) is not well-defined. The aim of this study was to determine the relationship of serum uric acid (SUA), inflammatory markers and CED. In this prospective cohort study, serum uric acid, hsCRP levels, and neutrophil count were measured in 229 postmenopausal women who underwent diagnostic catheterization, were found to have no obstructive CAD and underwent coronary microvascular function testing, to measure coronary blood flow (CBF) response to intracoronary acetylcholine.

The average age was 58 years (IQR 52, 66) years. Hypertension was present in 48%, type 2 diabetes mellitus in 5.6%, and hyperlipidemia in 61.8%. CED was diagnosed in 59% of postmenopausal women. Mean uric acid level was 4.7 ± 1.3 mg/dL. Postmenopausal women with CED had significantly higher SUA compared to patients without CED (4.9 ± 1.3 vs. 4.4 ± 1.3 mg/dL; p=0.02). There was a significant correlation between SUA and % change in CBF to acetylcholine (p=0.009), and this correlation persisted in multivariable analysis. SUA levels were significantly associated with increased neutrophil count (p=0.02) and hsCRP levels (p=0.006) among patients with CED, but not those without CED. Serum uric acid is associated with coronary microvascular endothelial dysfunction in postmenopausal women and may be related to inflammation. These findings link serum uric acid levels to early coronary atherosclerosis in postmenopausal women.

Keywords

uric acid; microvascular dysfunction; inflammation; postmenopausal; endothelial dysfunction; nonobstructive coronary artery disease

Corresponding Author. Amir Lerman MD, 200 1st St SW, Rochester MN, 507-284-2511, lerman.amir@mayo.edu.

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Background

Coronary artery disease (CAD) is a well-recognized leading cause of death in developed countries in both men and women. Premenopausal women have a lower cardiovascular risk when compared to men of the same age, and this is thought to be secondary to protective effects of estrogen. As estrogen levels decrease, cardiovascular risk may increase in postmenopausal women.(1, 2),

Elevated uric acid levels and inflammatory markers have been associated with a number of cardiovascular risk factors including hypertension, hyperlipidemia, obesity, and metabolic syndrome across the population but also in postmenopausal women.(3, 4) Serum uric acid levels are increased in women undergoing both natural and surgical menopause even after adjustment for potential confounders.(5) Uric acid has thus been studied in postmenopausal women and data shows that the absence of estrogen may be associated with hyperuricemia. (6) Additionally, higher levels of uric acid have been associated with increased coronary artery calcium deposits and progression of CAD, independent of other cardiovascular risk factors in postmenopausal women. (7) Uric acid has also been identified as an independent predictor of cardiovascular events.(7),(8) This may be secondary to inflammation as evidenced by increased inflammatory markers and oxidative stress, decreased release of endothelial nitric oxide, and evolution of endothelial dysfunction.(7),(9),(10) Interestingly, uric acid levels even at the upper limit of normal have been shown to be associated with increased cardiovascular risk. (11–16)

The mechanism explaining this association of uric acid and cardiovascular disease in patients with coronary endothelial dysfunction (CED) is poorly understood. Endothelial dysfunction, characterized by reduced nitric oxide activity, is an early phase of atherosclerosis and a predictor of cardiovascular events.(17–23),(24, 25) Preliminary data suggest peripheral endothelial dysfunction may be associated with elevated uric acid levels, however these findings are inconsistent. (24, 25),(26, 27) How uric acid may contribute to CED is unknown.

The association of elevated uric acid levels and peripheral endothelial dysfunction, CAD and all-cause mortality appears to be more pronounced in postmenopausal women.(8, 28),(29) Because increased inflammatory markers and uric acid levels are associated with CED and possibly increased cardiovascular risk, the aim of this study was to examine the relationship of serum uric acid, inflammation and CED in postmenopausal women and to assess predictors of coronary events in this population. We hypothesized that uric acid and inflammation were associated with endothelial dysfunction and adverse outcomes.

Methods

Patient population

Consecutive patients referred to Mayo Clinic between January 1992 and August 2012 for cardiac catheterization with no evidence of significant coronary artery disease on initial angiography were enrolled. All patients had blood work which included measurement of C-reactive protein, complete blood count with differential, basic chemistry panel, and uric acid

level. We excluded any patient that was not a postmenopausal female or had not completed baseline laboratory testing and index angiography with complete acetylcholine study. On enrollment, all patients completed a standardized validated questionnaire to assess baseline characteristics.(21, 30, 31) Menopausal status was assessed on enrollment via questionnaire, and based on primary physician diagnosis. A total of 229 subjects who underwent comprehensive coronary endothelial function assessment and basic laboratory assessment were analyzed. All patients had provided informed consent as part of study enrollment, but there was no specific consent obtained to analyze uric acid specifically. Only postmenopausal women with complete laboratory testing as well as index angiography with complete acetylcholine study were included. Patients with history of percutaneous coronary intervention, coronary artery bypass graft surgery, unstable angina pectoris, valvular heart disease, peripheral vascular disease, or known congestive heart failure were excluded from the study. The study was approved by the Mayo Clinic Institutional Review Board and all patients provided informed consent.

Coronary endothelial function assessment

Endothelium-dependent coronary vasoreactivity was assessed according to standardized protocol as previously described. (21, 31, 32) The Doppler guidewire was advanced within the coronary-infusion catheter and placed in the mid-left anterior descending coronary artery. Acetylcholine was administered in the left anterior descending artery at incremental doses for 3 minutes each with increasing concentrations. During each infusion, Doppler measurements, hemodynamic tracings and coronary angiogram were recorded to be subsequently analyzed by a blinded, independent investigator. Coronary artery diameter was measured by having an investigator measure the segment 6 mm distal to the Doppler wire tip using a computer based image system. The percent change in coronary blood flow (CBF) in response to acetylcholine was indicative of endothelium-dependent coronary flow reserve. Coronary endothelial dysfunction was defined as less than 50% increase in CBF with acetylcholine.(21, 33, 34)

Subsequent evaluation

All patients received a standardized questionnaire for assessment of their overall health several years after their index coronary angiogram and endothelial function study. The standardized questionnaire was used to assess occurrence of major adverse cardiovascular events including stroke, rehospitalization, myocardial infarction or death after a median follow-up of 6.3 years (IQR 3.5, 10.7). Responses were verified by medical record review conducted by an investigator blinded to the results of the standardized questionnaire.

Statistical analysis

All data are displayed as mean ± standard deviation. Variables that have skewed distribution are reported as median with first and third quartiles listed in parenthesis. Demographic and baseline clinical data were compared using Fisher’s Exact Test, ANOVA and Wilcoxon tests for continuous data and Pearson chi squared test for categorical data after adjustment for potential confounders including traditional cardiovascular risk factors.

Results

Baseline characteristics

A total of 229 postmenopausal women without epicardial stenosis on coronary angiography underwent microvascular function testing with graded infusion of acetylcholine. Average age was 58 years (IQR 52, 66) years. Hypertension was present in 48%, type 2 diabetes mellitus in 5.6%, and hyperlipidemia in 61.8%. Mean uric acid level was 4.7 ± 1.3 mg/dL.

CED was diagnosed in 59% of postmenopausal women on invasive acetylcholine testing. There was no significant difference in follow-up duration between patients with and without CED (p=0.96).

Coronary blood flow and Uric acid

Patients with CED had significantly higher levels of uric acid when compared to patients without CED (4.9 ± 1.3 mg/dL vs. 4.4 ± 1.3 mg/dL; p=0.03). There was a significant correlation between serum uric acid level (SUA) and percent change in CBF with acetylcholine (p=0.009) (Figure 1).

In a linear regression model, higher serum uric acid levels were significantly associated with higher neutrophil counts (p=0.01) (Figure 2), and higher hsCRP levels (p=0.006) in patients with CED (Figure 3). After adjustment for history of current estrogen use, glomerular filtration rate (GFR), hypertension, and body mass index (BMI), SUA remained significantly associated with CED (p=0.02). Neutrophil count and hsCRP were not significantly associated with CED.

Coronary blood flow and inflammatory markers

In a linear regression model, increasing uric acid levels were significantly associated with increased neutrophil count (p=0.01) (Figure 2), and increased hsCRP levels (p=0.006) (Figure 3) in patients with CED. Uric acid was not associated with increased levels of inflammatory markers in patients without CED (p>0.05). Higher SUA levels were associated with higher hsCRP in a linear regression model (R= 0.22; p=0.01).

Major Adverse Cardiovascular Events

Patients were followed for a median of 7 years (IQR 4, 11) for the development of major adverse cardiovascular events (MACE), which included stroke, cardiovascular death, myocardial infarction, and cardiovascular hospitalization. There were a total of 25 MACE, 16 occurring in patients with CED on baseline acetylcholine study and 9 in patients without CED. Baseline uric acid levels were significantly higher in patients who developed MACE than in patients who did not (5.2 (IQR 4.2, 6.7) vs. 4.4 (3.8, 5.4); p=0.008) (Figure 4). When stratifying by patients with and without CED, uric acid levels were only significantly associated with MACE in patients with CED. Uric acid was an independent predictor of MACE after adjustment for potential confounders including age, hypertension, diabetes, hyperlipidemia, body mass index, and estrogen (LR 8.9 p=0.003). Given potential association of lipid levels and fasting blood glucose, a separate multivariable regression adjusting for age, hypertension, glucose, uric acid, body mass index, HDL, LDL,

triglycerides, estrogen use, and antihypertensive use, showed that uric acid remained an independent predictor of major adverse cardiovascular events (LR 4.3, p=0.04).

Discussion

The current study demonstrates an association between serum uric acid, coronary microvascular endothelial dysfunction, inflammatory markers, and cardiovascular outcomes. We have three main findings. First, CED in postmenopausal women is independently associated with increased serum uric acid levels after adjustment for traditional risk factors. Second, higher uric acid levels were associated with higher levels of inflammatory markers in patients with CED, and higher inflammatory markers were in turn associated with a reduced response of CBF to acetylcholine. Third, baseline uric acid levels were higher in patients who developed MACE on follow-up, and uric acid was an independent predictor of MACE after adjusting for potential confounders. Higher uric acid levels at baseline may play a role in development of adverse cardiovascular outcomes, although the mechanisms for this are unclear. These findings suggest that serum uric acid levels are associated with CED and potentially progression of atherosclerosis mediated by uric acid and inflammation.

CED is increasingly recognized as an initial predisposing step for development of atherosclerosis. Recognition of risk factors for early coronary atherosclerosis and CED can be important in identifying and treating vulnerable patients who might develop CAD. (17, 18, 20, 35) While uric acid is a recognized risk factor in the development of cardiovascular disease, the mechanism is not well-understood.

Uric acid and cardiovascular risk factors

Several studies have suggested that uric acid is associated with traditional cardiovascular risk factors and major adverse cardiovascular events, and several mechanisms have been postulated to explain these associations, including inflammatory and vascular changes in the microcirculation, endothelial dysfunction and dysregulation of glucose uptake.(9, 10, 36), (37) Adverse outcomes of uric acid are independent of crystal formation, and so even normal levels of uric acid may be associated with adverse cardiovascular events. Several studies have shown that uric acid levels at the upper limit of normal can be associated with cardiovascular risk factors and mortality, and suggest that a lower threshold may be considered to prevent cardiovascular events. (11, 14, 15)

Serum uric acid has also been associated with endothelial dysfunction in several studies. Acikgoz and colleagues found that SUA levels were higher in patients with microvascular angina and that SUA levels were predictive of carotid atherosclerosis.(38) Increased hsCRP levels and reduced flow-mediated vasodilation have also been reported in patients with higher uric acid levels.(39) This association between elevated uric acid levels and reduction in flow-mediated vasodilation have been corroborated by other studies.(40),(41) The current study thus extends these previous observations and demonstrates for the first time the relationship between SUA and coronary endothelial function.

Uric acid levels also may be associated with hypertension, which in turn has been associated with endothelial dysfunction. Zoccali and colleagues studied a cohort of patients with

untreated essential hypertension reporting that uric acid levels were associated with endothelial dysfunction even after adjustment for potential confounders.(42) The role of hypertension is unclear, but given that hypertension may be associated with both microvascular dysfunction and uric acid levels, we adjusted for both hypertension as well as anti-hypertensive use, and found that uric acid remained an independent predictor of major adverse cardiovascular outcomes in this population. In a separate study of patients with untreated essential hypertension, inflammation was implicated as a potential key factor mediating the endothelial-renal function link.(43)

Treatment of hyperuricemia with allopurinol has been associated with improved cardiovascular outcomes, further supporting our findings.(44–46),(47) In a recent large prospective case-matched cohort study of patients with gout, urate-lowering therapy was found to improve overall cardiovascular outcomes.(47) Colchicine has also been shown to result in significant reduction in cardiovascular mortality in patients with gout. (48, 49)

Uric acid and CVD in women

Several studies have alluded to a sex-specific association between uric acid levels, inflammatory markers, early atherosclerosis and cardiovascular disease. Data suggest that the association between uric acid and cardiovascular risk factors and cardiovascular disease may be particularly prominent in postmenopausal women, further supporting our findings that CED is associated with increased uric acid levels and inflammation in postmenopausal women.(5, 50–53)

Hyperuricemia has been independently associated with non-invasive peripheral endothelial dysfunction in postmenopausal women.(40) Elevated uric acid levels have also been independently associated with increased coronary artery calcification in postmenopausal women without known cardiovascular risk factors and increased incident risk of MACE. (7), (8)

Potential mechanisms

There is a growing body of evidence suggesting an association between increased uric acid levels and postmenopausal status, and a causal link to increased cardiovascular risk in postmenopausal women. Endogenous estradiol plays a role in preserving endothelial function and in lowering serum uric acid level independent of cardiovascular risk factors, and with menopause, decreased estrogen levels and increased serum uric acid levels may promote endothelial dysfunction and development of cardiovascular disease.(5, 54–56) While the mechanism linking uric acid and cardiovascular disease has yet to be fully understood, it has been postulated that decreased estrogen levels may lead to increased uric acids levels, which in turn may cause endothelial dysfunction, predisposing patients to development of cardiovascular disease.(57)

Inflammation also plays a key role in the link between uric acid and endothelial dysfunction. (58–60) In the current study, we found that elevated inflammatory markers, including hsCRP and neutrophil count were associated with reduced percent change CBF with acetylcholine. Additionally, higher SUA levels were significantly associated with increased hsCRP and MACE in several studies of patients with CED, suggesting an association between

inflammation and endothelial dysfunction.(61–63) These findings are supported by previous data linking elevated inflammatory markers to elevated uric acid levels.(64) Data suggest that uric acid may induce both endothelial dysfunction and vessel inflammation which concomitantly may lead to accelerated atherosclerosis, likely explaining the increased MACE seen in patients with higher uric acid levels and CED.(39, 64, 65) Uric acid appears to exert a proinflammatory effect on endothelial cells, causing reduced nitric oxide bioavailability, and vascular smooth muscle cells, increasing chemokine and cytokine expression.(66, 67) Serum uric acid levels have also been suggested to be predictive of cardiovascular disease due to its sensitivity for underlying inflammation and remodeling within the arterial vessel wall.(68, 69) Lastly, serum uric acid has been shown to be linearly related with the activity of xanthine oxidase. Increased xanthine oxidase enzyme activity may be associated with a corresponding increased production of free oxygen radicals, potentially activating the atherosclerotic process.(70) This is further supported by studies showing that xanthine oxidase inhibition is associated with improved endothelial function, cardiovascular risk, and plaque progression in pre-clinical and clinical studies.(71–75).(76) Thus, xanthine oxidase activity and increased oxygen free radicals may play a key role in initiation and progression of atherosclerosis, even independent of uric acid. Our findings from the current study demonstrating an association between increased inflammatory markers, uric acid levels and impaired endothelial dysfunction are thus, consistent with these observations.(60)

Limitations

The findings are based upon cross-sectional data at initial presentation. A temporal association between uric acid and development of endothelial dysfunction cannot be inferred with certainty. Our data regarding outcomes in these patients were obtained via a questionnaire-based method, which inherently could be biased and cause an overall underestimation of the number of events in each group. Additionally, we do not have data describing the length of antihypertensive therapy in these patients, and this could have a potential effect on endothelial function. To best address this, we have adjusted for use of antihypertensive medications in our analysis. Lastly, menopausal status was assessed by questionnaire and thus hormonal levels are not available.

Conclusion

Increased serum uric acid levels are associated with coronary microvascular endothelial dysfunction and increased inflammatory markers in postmenopausal women. Detection of markers of inflammation including uric acid may be useful in understanding the mechanism and predicting progression of patients with nonobstructive coronary artery disease and atherosclerosis. Moreover, further investigation is necessary to explore the utility of lowering uric acid levels in risk factor modification and attenuation of non-obstructive coronary disease and atherosclerosis.

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Conflicts of Interest and Relevant Relationships with Industry:

Dr. Amir Lerman is a member of the advisory board of Itamar Medical, a company that produces EndoPAT, a device for noninvasive endothelial function detection. This device was not used in this study. Dr. Lilach O Lerman is his spouse.

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Perspectives

In postmenopausal women with nonobstructive women, we find that uric acid levels are higher in those with elevated inflammatory markers and coronary microvascular dysfunction. Moreover, serum uric acid levels appeared to be associated with increased major adverse cardiovascular events. Further investigation is necessary to explore the role of uric acid and uric acid lowering therapies in management of cardiovascular risk in postmenopausal women.

Novelty and Significance

1. What is New
   - **a.** Coronary microvascular dysfunction and endothelial dysfunction are associated with increased serum uric acid levels.
   - **b.** Higher serum uric acid levels were significantly associated with increased hsCRP and major adverse cardiovascular events in patients with CED
2. What is Relevant
   - **a.** Elevated uric acid levels may be a maker of increased cardiovascular risk secondary to underlying coronary microvascular dysfunction and increased inflammation.
3. Summary
   - **a.** Increased serum uric acid levels are associated with coronary microvascular dysfunction and increased inflammatory markers.
   - **b.** Increased serum uric acid levels are associated with increased major adverse cardiovascular events in postmenopausal women.
   - **c.** Measurement of uric acid and uric acid lowering therapy may have a role in management of postmenopausal women's cardiovascular risk.

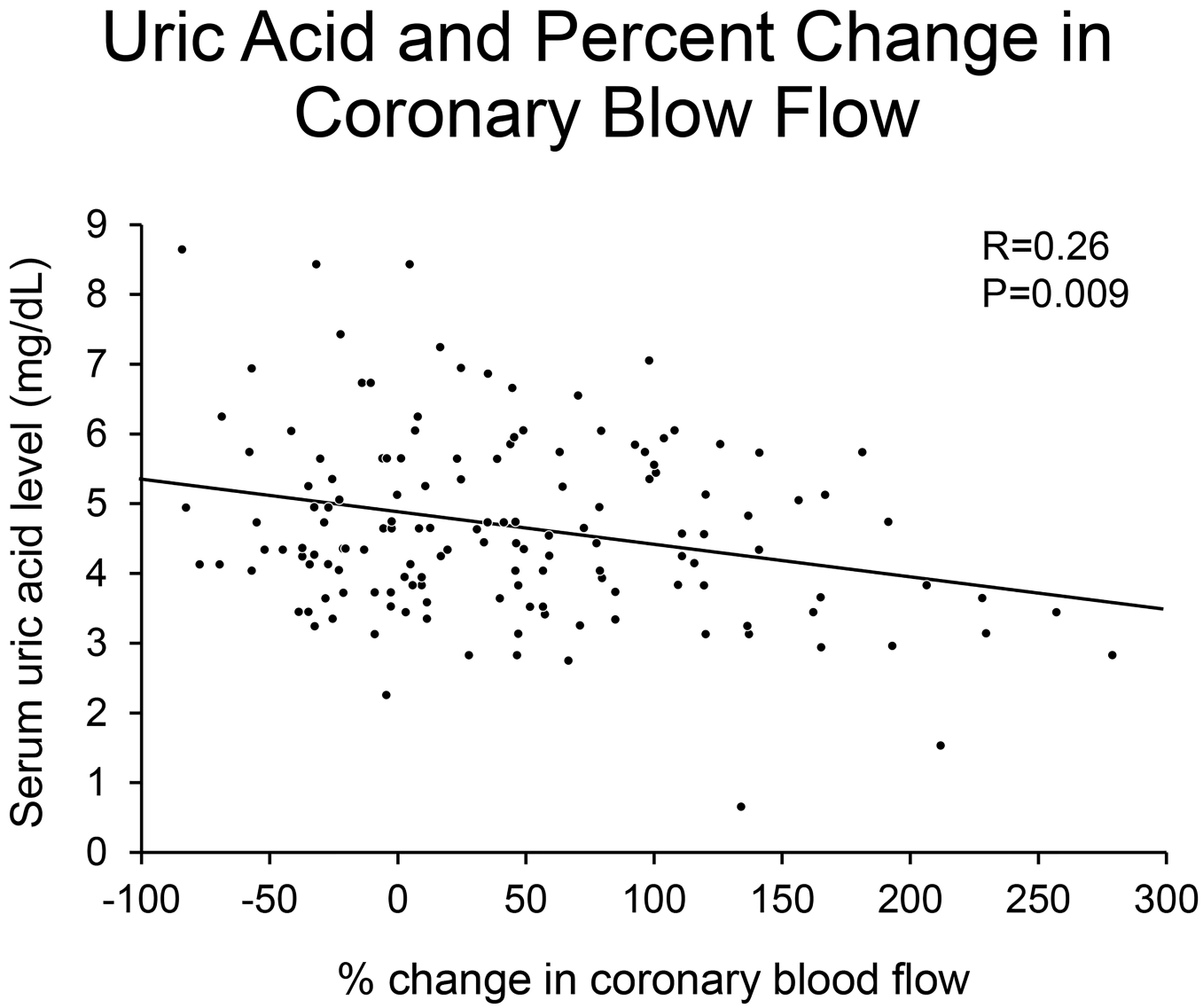

Figure 1. Uric acid and percent change in coronary blood flow

Figure 1 shows that increased serum uric acid levels are associated with decreased percent change in coronary blood flow and worse endothelial function.

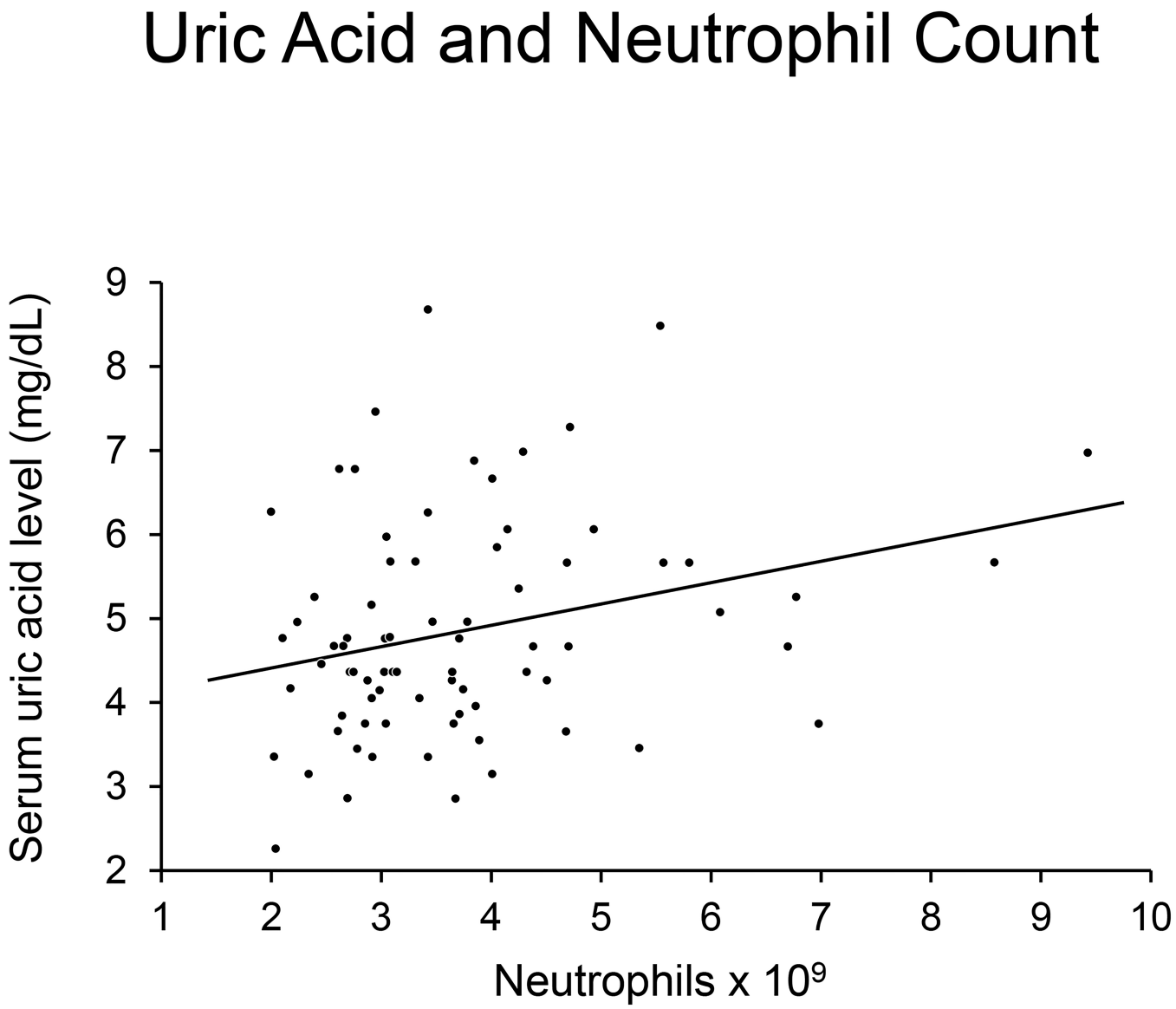

Figure 2.
Figure 2 shows that neutrophil counts increase with increasing serum uric acid levels.

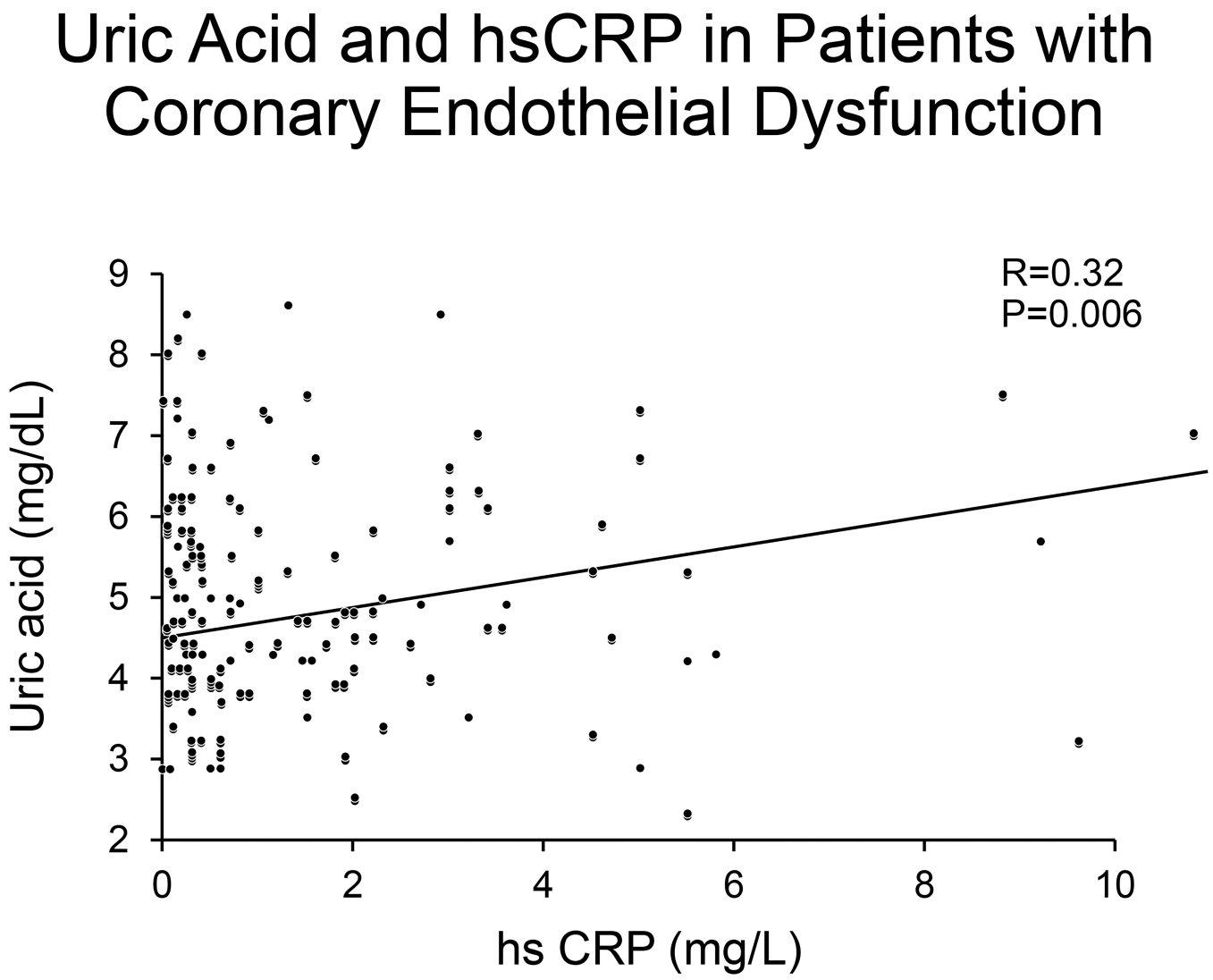

Figure 3. Uric acid and hsCRP in patients with Coronary Endothelial Dysfunction

Figure 3 shows that increasing hsCRP levels are associated with increased uric acid levels.

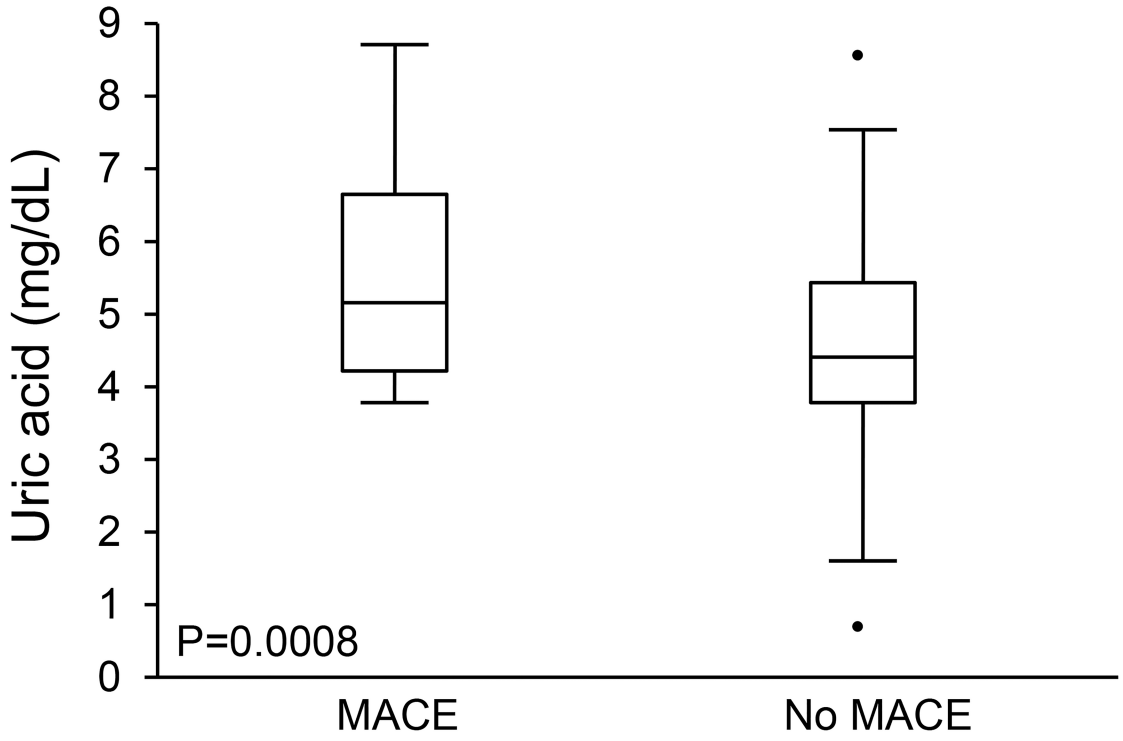

Figure 4. Uric acid and Development of Major Adverse Cardiovascular Events (MACE)
Patients who developed MACE on follow-up had significantly higher uric acid levels than patients who did not develop MACE.

Table 1

Baseline characteristics in 229 postmenopausal women undergoing coronary blood flow (CBF) response to intracoronary acetylcholine

Variable	CMD (n=133)	No CMD (n=88)
Age (years)	57 (IQR 51–65)	58 (53–67)
Diabetes	6.0% (8)	3.4% (14)
Hypertension	50.0% (66)	46.1% (41)
Hyperlipidemia	63.6% (84)	60.9% (53)
Body mass index (kg/m^2)	28.1 (IQR 24.2,31.9)	27.2 (IQR 23.8,31.6)
Neutrophils (×10^9)	3.4(2.8,4.3)	3.8 (3.0,4.7)
hsCRP (mg/L)	0.6 (0.3,2.0)	0.4(0.2,1.6)
Uric acid (mg/dL)	4.7(4.1, 5.7)	4.3 (3.5,5.5)
Antihypertensive use	20.0% (27)	21.3%(19)
Follow-up duration (years)	6.2 (3.8, 10.1)	6.5 (3.2,11.5)

CMD = coronary microvascular dysfunction; hsCRP = high sensitivity C-reactive protein