Review

Angiology
2022, Vol. 73(1) 9–17

DOI: 10.1177/00033197211012546
journals.sagepub.com/home/ang
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The Role of Uric Acid in the Acute Myocardial Infarction: A Narrative Review

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Abstract

Increased serum uric acid (SUA) levels have been associated with various pathologic processes such as increased oxidative stress, inflammation, and endothelial dysfunction. Thus, it is not surprising that increased SUA is associated with various adverse outcomes including cardiovascular (CV) diseases. Recent epidemiological evidence suggests that increased SUA may be related to acute myocardial infarction (AMI). Accumulating data also showed that elevated UA has pathophysiological role in the development of AMI. However, there are also studies showing that SUA is not related to the risk of AMI. In this narrative review, we summarized the recent literature data regarding SUA and AMI after providing some background information for the association between UA and coronary artery disease. Future studies will show whether decreasing SUA levels is beneficial for outcomes related to AMI and the optimum SUA levels for best outcomes in CV diseases.

Keywords

uric acid, coronary artery disease, inflammation, kidney disease, myocardial infarction

Introduction

Uric acid (UA) is the final product of purine metabolism in humans and is produced by xanthine oxidase (XO), an enzyme which is also a source of reactive oxygen species (ROS) in the cardiovascular (CV) system.[1] Xanthine oxidase is a ubiquitous enzyme found in various organs of the body, but UA is mainly produced by the liver and excreted by the kidneys and the intestinal tract.[2,3] In the myocardium, the XO is mostly localized in capillary endothelial cells.[4]

Uric acid has been a topic of discussion due to its controversial functions in the CV system related to the evolutionary process of its metabolism. Circulating UA levels in humans are 3 to 10 times higher than in other mammals due to genetic mutations in the enzyme uricase. Uricase substantially decreases plasma UA levels in other mammals by converting UA to allantoin.[2] This evolutionary process is thought to be protective against oxidative damage and more efficient to maintain blood pressure under low-salt dietary conditions. However, an increase in circulating UA levels, to which the Western lifestyle and diet also contribute, has become a detrimental factor to CV health in humans.[5,6] Various factors can affect serum uric acid (SUA) levels, and some of them by either causing overproduction of UA or reducing the excretion of UA can result in hyperuricemia in humans (see Table 1).

Elevated SUA levels are associated with hypertension,[7,8] heart failure,[9] stroke, obesity, metabolic syndrome, diabetes, chronic kidney disease (CKD), and nonalcoholic fatty liver disease.[2,10-15] Because of this mutual relationship between UA and other CV risk factors, the independent role of SUA in the development of coronary artery disease (CAD) and the potential relationship between UA and CAD have been topics of controversy for many years.[15-17] Some current evidence, including data from the Framingham Heart Study group,[18] did

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Table 1. Modifiable Causes of Hyperuricemia.

Decreased uric acid excretion
Medications (eg, pyrazinamide, aspirin, loop diuretics, thiazides, niacin)
Chronic renal insufficiency, lead nephropathy
Ketoacidosis (eg, due to starvation or diabetes mellitus)
Lactic acidosis
Postmenopause
Increased uric acid production
Tumor lysis syndrome
Hemolytic anemia
Psoriasis
Myeloproliferative neoplasms
Chemotherapy, radiation
Lesch-Nyhan syndrome
Phosphoribosyl pyrophosphate synthetase overactivity
von Gierke disease
Diet rich in protein, purine, and fructose
Obesity
Hypercholesterolemia, hypertriglyceridemia
Hypertension
Sleep apnea
High alcohol consumption

not show SUA as an independent risk factor for CAD,[18,19] even though several large epidemiological studies support that SUA is both an independent risk factor for CAD and a predictor of mortality and adverse outcomes related to CAD.[20-23]

A meta-analysis including >400 000 participants in a total of 26 prospective cohort studies showed an independent relationship between increased SUA levels and CAD mortality; a 1 mg/dL increase in SUA was associated with a 12% increase in the overall risk of death due to CAD.[24] A recent study with >20 000 participants also found higher dietary uricemia is related to higher all-cause and CV mortality even after adjustments for body mass index, hypertension, and type 2 diabetes mellitus, suggesting dietary interventions to reduce SUA levels may reduce all-cause and CV mortality.[25] Although there are contradictory findings for the relationship between SUA and acute myocardial infarction (AMI), accumulating evidence indicated higher SUA levels could be related to several adverse outcomes related to AMI. In the article, we elucidate this relationship between SUA and AMI after discussing the suggested mechanisms of UA on the development of CAD as a narrative review.

Search Strategy

We searched Pubmed, MEDLINE, and Embase for literature published from January 1, 2010, to September 1, 2020, written in English. We used the following key terms: "uric acid," "coronary artery disease," "myocardial infarction," "adverse outcome," "inflammation," "endothelial function," and "cardiovascular disease." A narrative review was performed giving priority to more recent, widely cited publications, guided by the authors' experience.

The Role of UA in the Development of CAD

Even though elevated SUA concentrations are strongly associated with CAD in several studies, the exact mechanism involved in the association between UA and CAD has not been fully demonstrated. Several studies have shown that UA could penetrate endothelial cells and could have numerous pathophysiological effects, such as promotion of oxidative stress, depletion of nitric oxide (NO) and worsening endothelial function, induction of both local and systemic inflammation, proliferation of vascular smooth muscle cells, and vasoconstriction.[5,26,27] Clinical and biochemical studies have also shown that it is not only UA itself but also the process of generating UA by the enzyme XO, which generates ROS, contribute to the pathogenesis of CAD.[4,28] Moreover, UA is produced by consuming adenosine triphosphate (ATP), which suggests that increased UA partially means ATP depletion.[13] Uric acid induces mitochondrial dysfunction and superoxide generation through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, thus depleting energy (ATP) capacity.[13]

The relationship between UA and CAD may also be explained in the context of renin–angiotensin system (RAS) activation. Uric acid may cause abnormal RAS activation by upregulating the tissue RAS expression via Toll-like receptor 2/4 in adipocytes, which is also related to increased oxidative stress and the pathogenesis of CAD.[29] Several animal experiments and observational studies pointed out that decreasing SUA levels could reduce RAS activity, related renal injury, and blood pressure; however, a randomized controlled trial (RCT) failed to show any effect on RAS activity or blood pressure after 8 weeks on UA-lowering therapy.[30]

The relationship between fibroblast growth factor 23 (FGF23) and UA is also worth a mention. Several studies showed a positive correlation between SUA and FGF23 levels in healthy individuals, patients with CKD, and renal transplant patients.[31,32] The mechanism of this association between SUA and FGF23 is unknown but argued as effects of FGF23 by either decreasing renal urate clearance or inhibiting vitamin D metabolism.[11] FGF23 may be involved in the atherosclerotic process (especially vascular calcification), and several studies demonstrated an independent association between FGF23 and CAD as well as with the cumulative number of stenotic vessels.[33]

Oxidative and Antioxidative Properties of UA

Even though UA contributes significantly to the antioxidant reserve of the body, it is also associated with oxidative stress.[34] These paradoxical actions of UA arise from its solubility, which is mainly dependent on the pH of the environment (more soluble in elevated pH), and the location (extracellular protection vs intracellular damage).[35] If UA becomes insoluble by crystallization, it can activate the immune system and act as a pro-oxidant, location-independent, molecule. On the other hand, soluble UA can act as an antioxidant extracellularly (within plasma) and as a pro-oxidant intracellularly. The

chemical structure of soluble UA makes it highly reactive with oxygen radicals including singlet oxygen, superoxide, peroxyl, and hydroxyl radicals and ensures its antioxidant functions, which protects the vascular endothelial cells from external oxidative stress, such as ROS produced by activated granulocytes during reperfusion injury.[5] Besides its direct pro-oxidant role intracellularly, UA may also be an indicator of increased XO activity, which is one of the major producers of ROS in the CV system. It has also been shown that XO and NADPH oxidase are closely related to ROS producers and that they can mutually activate each other.[36]

Uric acid is likely to play a role in the progression of the atherosclerotic plaque in coronary arteries, by acting as a pro-oxidant that promotes lipoprotein oxidation; atherosclerotic plaques contain significant amounts of UA.[37,38] It has also been suggested that elevated SUA levels may promote coronary thrombus formation[39] by inducing low-density lipoprotein cholesterol oxidation and the peroxidation of lipids, promoting platelet aggregation, and the formation of UA crystals, which could damage tunica intima of arteries.[40]

Inflammation and UA

A recent study with higher than 23 000 participants suggested participants with better CV health scores had lower SUA and inflammatory markers.[41] The pathogenesis of gout disease implicates that mono-sodium urate crystals promote the inflammatory response by activating the NLR (nucleotide-binding oligomerization domain-like receptors) family pyrin domain containing 3 (NLRP3) inflammasome in macrophages and trigger inflammatory caspases and pro-interleukin (IL)-1β production.[42] In addition, it was recently reported that soluble UA without crystal formation can activate the NLRP3 inflammasome and induce IL-1β production by redox states changes with mitochondrial ROS production in macrophages.[35] Recent studies have also demonstrated a role of the NLRP3 activation in the development of renal inflammation and renal fibrosis.[35] Several studies showed there is a significant association between UA and inflammatory markers, such as neutrophil count, C-reactive protein, IL-6, IL-1ra, IL-18, and tumor necrosis factor -α.[43] The association between UA and inflammation has also been suggested in a study which concluded that UA could act as a pro-inflammatory DAMP (damage-associated molecular patterns) because they found that UA depletion (intracellularly from dying cells or extracellularly after cell death) selectively inhibits the cell death–induced inflammation.[44]

Since inflammation has a significant role in the pathogenesis of CAD, in vivo and preclinical studies inferred that NLRP3 inflammasome activation by UA plays a role in the progression of CAD.[45]

Depletion of NO and Endothelial Dysfunction

Elevated levels of UA are associated with endothelial dysfunction by reducing NO bioavailability.[5] Intracellular UA could affect NO bioavailability via several mechanisms such as blocking the uptake of L-arginine, stimulating L-arginine degradation via arginase and directly scavenging NO.[5]

Additionally, UA causes activation of the high mobility group box 1/receptor for advanced glycation end products signaling pathway, which increases inflammatory cytokines.[46] Inflammation with chronic hypoxia further induces the XO enzyme augmenting SUA levels and ROS, which leads to endothelial dysfunction.[36,47-49] Increased oxidative stress, inflammation, and endothelial dysfunction result in vascular smooth muscle cell proliferation and vasoconstriction, which deepens the tissue hypoxia even more, so those effects of UA on endothelium promote each other, resulting in a vicious cycle illustrated in Figure 1.

Uric Acid and Acute Myocardial Infarction

The Uric Acid Right for Health (URRAH) study included 23 467 individuals and concluded that SUA is an independent risk factor for fatal AMI even after adjusting for possible confounders.[39] The authors speculated that routine screening of SUA levels could be useful as a predictor for acute CV events.

Early studies by Lazzeri et al[50,51] conflicted with each other about an independent association of UA with in-hospital mortality after an AMI. Other studies failed to demonstrate an association between UA levels and in-hospital or midterm mortality after AMI.[52] However, several other studies showed that elevated UA levels independently predict poor clinical outcomes after AMI, including the development of heart failure, major adverse CV events (MACE), increased in-hospital mortality, increased 1-year mortality, and increased long-term mortality and morbidity.[53,54] Kaya et al[55] have also shown that high UA levels on admission are an independent prognostic factor for short- and long-term adverse outcomes in patients with AMI treated with primary percutaneous coronary intervention (PCI). Furthermore, a recent meta-analysis, including 13 studies (9371 patients) suggested that even higher UA levels within the normal range could be an indicator of short-term mortality after AMI in patients who were treated with primary PCI.[56] A recent study with 3202 patients with CAD who had PCI also showed that patients who had high SUA SD had a higher risk of MACE, AMI, total major CV events, and CV death, suggesting high SUA variability is also associated with higher future CV events after PCI.[57]

Mandurino-Mirizzi et al suggested that elevated levels of SUA are associated with larger acute infarct size during an AMI and unfavorable clinical outcomes, which may be related to the effects of UA on endothelial dysfunction. Although an elevated SUA may induce larger acute infarct size, the study concluded that there is no further impairment in the repairing phase as infarct size shrinkage is similar compared with patients who have normal SUA levels.[58] Kojima et al[59] suggested that patients with hyperuricemia with an AMI have a higher rate of left ventricular systolic and diastolic dysfunction, as well as MACE (including heart failure, death), possibly because UA could increase oxidative stress and inflammation

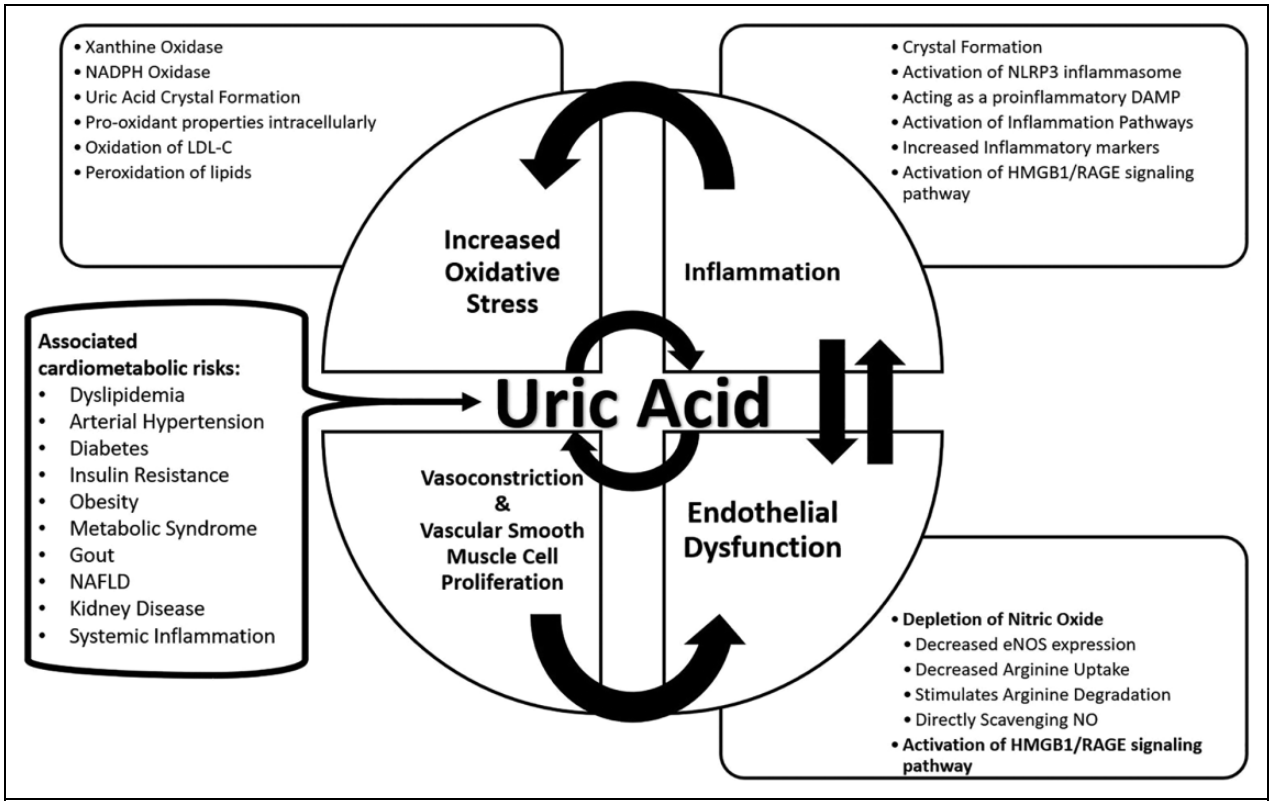

Figure 1. Postulated mechanisms for association between uric acid and coronary artery disease. DAMP indicates damage-associated molecular patterns; eNOS, endothelial nitric oxide synthetase; HMGB1/RAGE, high mobility group box 1/receptor for advanced glycation end products; LDL-C, low-density lipoprotein cholesterol; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, nonalcoholic fatty liver disease; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide.

inducing cardiomyocyte apoptosis with further myocardial remodeling.

A number of studies have compared the mortality rates between different SUA quartiles, with a meta-analysis concluding that there is a 2- to 4-fold increase in mortality of patients in the fourth quartile compared with those in the lower quartiles.[60] Several studies have suggested a threshold effect of SUA and concluded that the best cutoff value for SUA level in order to predict mortality in patients with an AMI as >7,[61] >7.5,[62] >7.52,[59] and >6 mg/dL.[63] Furthermore, the URRAH study demonstrated a prognostic cutoff value of >5.70 mg/dL to discriminate patients with risk of complications after an AMI and those free from complications.[39]

The Killip classification is a well-established prognostic indicator of heart failure after an AMI. Several studies have shown that there is a correlation between SUA concentrations and the Killip classification,[59] suggesting that SUA levels may be a marker of risk stratification after an AMI.[64]

During an AMI, tissue hypoperfusion causes hypoxia, which promotes the activity of XO and increases both SUA concentrations and oxidative stress. Elevated SUA also has direct detrimental effects, as discussed earlier, by initiating oxidative stress and inflammation, reducing NO production, thus causing endothelial dysfunction, further contributing to worsening tissue ischemia, myocardial necrosis, remodeling, and ultimately the development of poorer clinical outcomes after an AMI. However, UA may also have beneficial effects during an AMI related to its antioxidant properties; this Janus-type effect may explain some of the discrepant findings.

Effects of SUA-Lowering Therapies on Patients With CAD

Several studies focused on the effects of SUA-lowering therapies on reducing the incidence of CAD and its associated mortality. The SUA-lowering treatment options include uricostatic drugs (eg, allopurinol and febuxostat), which inhibit XO, and uricosuric drugs (eg, probenecid and lesinurad), which interfere the reabsorption of UA by the kidneys.[28]

Lowering SUA levels by uricosuric drugs can alleviate the detrimental effects of high SUA levels on the vascular endothelium, blood pressure, and inflammation.[48,65,66] Two interventional studies (the GREek Atorvastatin and Coronary Heart Disease Evaluation [GREACE][67] and the Losartan Intervention For Endpoint reduction in hypertension [LIFE][68]) found that decreasing SUA levels by atorvastatin and losartan, which have uricosuric actions, is associated with attenuation of CV events. The GREACE study concluded that the patient group who received a more aggressive statin treatment, which resulted in an average 0.8 mg/dL lower SUA levels, had significantly

lower CV events than patients treated with lower statin doses.[67] The LIFE study showed that both baseline and in-study SUA levels were associated with the incident of CV events and losartan rather than atenolol treatment provided 29% of the benefit in terms of CV risk, which could be attributed to the decrease in SUA levels by losartan.[68] Several similar studies also showed similar effects of statins on SUA and CV events.[69,70]

Uricostatic agents (eg, allopurinol, febuxostat), which are the first-line treatment for hyperuricemia, are associated with improved endothelial function and reduced inflammation.[48] Several clinical studies show that UA-lowering treatment with XO inhibitors has potential CV protective effects.[4] Goicoechea et al[71] concluded that long-term allopurinol treatment in patients with CKD could reduce the CV risk. A recent meta-analysis including 670 individuals from 10 RCTs pointed out significant beneficial effects of allopurinol treatment on endothelial function independently from SUA levels.[72]

There are contradictory findings of UA-lowering treatments on the risk reduction of MI, with some studies suggesting that allopurinol treatment may be associated with increased risk of MI and poor outcomes.[73,74] However, several other studies have shown that allopurinol treatment is associated with the risk reduction of MI. Two different case–control studies concluded that allopurinol treatment may reduce the risk of first-time nonfatal AMI, with an OR of 0.52 (95% CI, 0.33-0.83)[75] and 0.80 (95% CI, 0.59-0.99)[76] suggesting that allopurinol may have cardioprotective effects.

Jasvinder et al[77] showed that patients with gout and diabetes who are current users of allopurinol had a significantly lower risk of incident MI, with an HR of 0.67 (95% CI, 0.53-0.84). Another retrospective cohort study, which included new allopurinol users (n = 28 488) among a 5% random sample of Medicare beneficiaries from 2006 to 2012 to investigate the first incidence of MI after initiation of allopurinol, found that allopurinol usage is associated with 15% decreased risk of incident MI (HR 0.85; 95% CI, 0.77-0.95).[78] A large cohort study of veterans with high SUA levels suggested that the use of allopurinol treatment may have significant survival benefits among patients with hyperuricemia, with a 23% lower all-cause mortality rate.[79] Wei et al[80] also showed that higher doses of allopurinol were associated with higher risk reduction in CV events and all-cause mortality.

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial compared effects of allopurinol and febuxostat on the mortality of 6190 patients with a history of gout and CV disease. In this trial, all-cause and CV mortality were higher in the febuxostat group than in the allopurinol group (all-cause mortality HR of 1.22 [95% CI, 1.01-1.47]; CV mortality HR of 1.34 [95% CI, 1.03-1.73]).[81] However, several limitations of the CARES trial should be noted including high discontinuation rates for treatment (56.6%) and follow-up visits (45.0%), lack of data on temporal course, and severity of gout flares, inconsistent findings between fatal and nonfatal CV end points.[82,83] The Febuxostat versus Allopurinol Streamlined Trial (FAST) argued against the findings of the CARES trial and showed that treatment with febuxostat was not associated with higher CV and all-cause mortality with better study design and ascertainment of events.[84]

Since the role of UA in the pathogenesis of atherosclerosis is complex, the mechanism(s) by which UA-lowering therapies may reduce the CV risk are also likely to be complex. In an animal study, it was suggested that the direct antioxidant effects of allopurinol may improve cardiac contractile function and prevent left ventricle remodeling in experimental congestive heart failure.[85] A recent meta-analysis including 12 studies (n = 197 patients with chronic heart failure [CHF], n= 183 patients with CKD) showed that allopurinol helped improve endothelial function in patients with CHF or CKD.[86] These properties of allopurinol could be responsible for its beneficial effects on CV system because both endothelial function and cardiac function are independent predictors of mortality. In RCTs, it has been shown that allopurinol has anti-ischemic actions in patients with stable angina by reducing myocardial oxygen consumption[87] and substantially lowering blood pressure.[66] Moreover, allopurinol could interfere with macrophage IL-1β secretion via the activation of NLRP3 inflammasome. All those effects of allopurinol are potential mechanisms for its cardioprotective effects. Besides SUA-lowering therapies, novel therapeutic agents that could target the NLRP3 inflammasome pathway or IL-1β would be expected to have beneficial effects on gout-associated CAD.

Target Level for UA

Even though there is no universal agreement on the optimal SUA levels, several guidelines accept the goal of treatment is to keep these levels <6.0 mg/dL in women and <7.0 mg/dL in men.[88] Generally, 2.6 to 5.7 mg/dL in premenopausal women and 3.5 to 7.0 mg/dL in men and postmenopausal women are accepted as normal SUA range levels in many countries.[88] However, high SUA levels even in the normal range could be a risk factor for hypertension, dyslipidemia, and CKD. Kuwabara et al[89] concluded that SUA levels, which are <5 mg/dL for men and <2 to 4 mg/dL for women, are the optimal range associated with the lowest risk for cardiometabolic diseases in a healthy population. However, there is no concrete evidence to treat asymptomatic hyperuricemia in a healthy population.

As discussed earlier, several studies defined 7 mg/dL SUA level as the cutoff value for the increase in the CV mortality and morbidity; however, the question of whether or not patients with high SUA should be treated in the case of additional CV risks or other diseases remains unknown. An RCT to investigate the effects of lowering SUA levels in patients with other CV risk factors or diseases should be conducted. Even though a variety of studies investigated different UA-lowering therapies effects on CV health in patients with CV events or other diseases, we do not certainly know when, or indeed how, to treat asymptomatic hyperuricemia.

Lifestyle changes, such as decreasing fructose intake,[90] to reduce SUA levels could be an option for patients with

hyperuricemia without any symptoms. However, there is no solid evidence to advise lifestyle changes for those patients or show their efficacy. Benefits of several drugs, such as atorvastatin, losartan, and allopurinol, on CV health have been presented earlier. However, there is no guideline or suggestion for those drugs to be used to reduce high SUA levels in order to decrease CV risks.

On the other hand, it should be kept in mind that the association between SUA levels and the cardiometabolic diseases is not valid for patients with hypouricemia (<2 mg/dL),[89] so there is no recommendation to reduce SUA levels <2 mg/dL due to potential adverse effects including an increase in CV risk and mortality, which is suggested as a U-shaped association between SUA and CV mortality in malnourished older people.[91] It has been also suggested that very low SUA levels could be associated with deterioration in cognitive function and the progression of dementia.[92] However, there is not enough evidence to conclude anything about the negative effects of hypouricemia due to the lack of cohort studies and evaluation of long-term effects in outcomes such as dementia, CV disease, and mortality.

Conclusions

An elevated level of UA has been associated with various pathologic processes such as increased oxidative stress, inflammation, and endothelial dysfunction. Thus, it is not surprising that increased UA is associated with various adverse outcomes, including CV diseases. Recent epidemiologic studies suggest that increased UA may be related to AMI. There are also concerns that elevated UA has a pathophysiological role in the development of AMI. Future studies are warranted on whether decreasing UA will be beneficial in AMI and the optimum UA levels for best outcomes in AMI.

Author Contribution

All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

This article does not include any studies with human participants or animals performed by any of the authors.

Acknowledgments

MK gratefully thanks the use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency of Turkey, Presidency of Strategy and Budget.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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