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Serum Uric Acid to Creatinine Ratio as a Predictor of Coronary Heart Disease: A Research Update

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ABSTRACT

Serum uric acid (SUA), the end-product of purine metabolism, functions as an important antioxidant and participates in multiple metabolic pathways. Accumulating evidence has demonstrated that SUA is closely associated with the initiation and progression of cardiovascular events and is considered an independent predictor of various vascular diseases. Elevated SUA can induce vascular endothelial dysfunction, accelerate atherogenesis and ultimately result in coronary heart disease (CHD). However, SUA concentrations are largely influenced by renal function; consequently, impaired renal function frequently increases SUA levels and limits the ability of SUA alone to reflect the true metabolic burden. Recently, the SUA-to-creatinine ratio (SUA/Cr), which normalizes SUA for renal function, has been proposed as a superior indicator of net SUA production. Thus, SUA/Cr provides a more accurate prediction of coronary artery disease severity in patients with CHD.Click here and insert your abstract text.

1. Introduction

Cardiovascular diseases (CVD) remain a major threat to human life and health, characterized by high incidence and mortality. Their impact on individuals and society is escalating, constituting a critical global public-health challenge. Among CVD, CHD is one of the dominant entities. Beyond traditional risk factors such as hyperlipidaemia, smoking and diabetes, novel cardiovascular risk biomarkers—including the serum SUA/Cr ratio—have recently emerged. Accumulating evidence links SUA/Cr with distinctive metabolic signatures [1]; however, a systematic delineation of its underlying mechanisms is lacking. The present review synthesizes current knowledge on the contributory roles of SUA/Cr in the initiation and progression of CHD from the perspectives of cellular inflammatory response, oxidative stress, insulin resistance and the renin–angiotensin–aldosterone system (RAAS), thereby providing a theoretical framework for future clinical translation.

2. Overview of CHD

CHD is a clinical syndrome caused by coronary stenosis or obstruction that impairs myocardial perfusion, leading to ischemia, hypoxia and even necrosis of cardiomyocytes. Its incidence is rising year by year and patients are becoming younger; most present with chest tightness, chest pain and dyspnea, which seriously impair quality of life. Early prediction and effective prevention therefore exert a critical influence on clinical outcomes. CHD results from the interplay of multiple factors, including pathological conditions and unhealthy lifestyles [2] below. Atherosclerosis—the principal etiology of CHD—is essentially a chronic inflammatory process that, driven by various risk factors, progressively thickens the arterial wall, narrows the vascular lumen and restricts blood flow [3].

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3. SUA/Cr Contributes to Coronary Artery Disease via Multiple Metabolic Pathways

3.1. Oxidative stress pathway

Oxidative stress represents the initiating stage of atherosclerosis. It is defined as a pathological condition in which the generation of reactive oxygen species (ROS) under harmful stimuli exceeds the intrinsic scavenging capacity, leading to cellular and tissue injury [4]. Oxidative stress is the major mechanism underlying endothelial dysfunction and is recognised as an early contributor to the development and progression of atherosclerotic diseases. Dynamic monitoring of oxidative stress biomarkers can provide important evidence for CHD risk assessment; abnormal changes in these markers often appear before clinical symptoms and thus serve as early predictors of CHD [5].

SUA is the end-product of purine metabolism in humans. SUA promotes the formation of superoxide anion (O_2^-), supplies substrate for peroxynitrite ($ONOO^-$) generation, indirectly amplifies lipid peroxidation and possesses direct pro-atherogenic potential [6]. An elevated SUA/Cr ratio usually reflects increased purine metabolism, which can over-activate xanthine oxidase and result in excessive SUA production. This process further stimulates massive generation of ROS such as O_2^- and hydrogen peroxide (H_2O_2), disrupting the oxidant–antioxidant balance [7]. ROS oxidise low-density lipoprotein (LDL) to oxidised LDL (OX-LDL); sub-endothelial macrophages take up OX-LDL via scavenger receptors and transform into foam cells. These foam cells not only synthesise and secrete multiple pro-inflammatory mediators but also release chemotactic factors that recruit leukocytes and amplify local inflammatory signals. Cytokines derived from foam cells stimulate smooth muscle cells to migrate into the intima and switch to a synthetic phenotype, secreting collagen and other extracellular matrix components that form the fibrous cap. Meanwhile, ROS inhibit synthesis of the vasodilator nitric oxide (NO) and reduce its bioavailability, thereby removing the "brake" on platelets and up-regulating the cyclo-oxygenase-1/thromboxane A_2 (COX-1/TXA_2) pathway, which increases platelet aggregation, promotes thrombosis, aggravates vascular injury and drives the formation and progression of atherosclerotic plaques [8][9]. Therefore, the SUA/Cr ratio can represent the systemic oxidative and metabolic status and reflect the severity of coronary artery lesions [10].

3.2. Inflammatory pathway

Inflammation is the core driver throughout the entire course of atherosclerosis. An elevated SUA/Cr ratio promotes vascular smooth muscle cell proliferation and induces inflammatory responses [11]. Numerous studies have confirmed a close relationship between coronary lesions and inflammation. Emerging evidence indicates that the novel inflammatory–metabolic biomarker SUA/Cr can serve as a potential predictor of early major adverse cardiovascular events and early therapeutic intervention in patients with ST-segment elevation myocardial infarction and multi-vessel coronary artery disease within one month [12]. As a net production index of SUA, SUA/Cr acts as a "biological danger signal". When cells undergo necrosis, the high intracellular concentration of uric acid is passively released into the extracellular milieu, forming urate crystals that are recognised by Toll-like receptors 2, 4 and 6 (TLR2, TLR4, TLR6). This triggers downstream nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signalling pathways. NF-κB enhances transcription of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) gene and generates mature pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18, amplifying inflammation. MAPK activation increases expression of monocyte chemoattractant protein-1 (MCP-1), a key chemokine in atherosclerosis progression, accelerating inflammatory responses and creating an inflammatory storm that promotes the onset and evolution of CHD [13][14][15]. A prospective study demonstrated a linear positive correlation between SUA/Cr and C-reactive protein (CRP), an established marker used in cardiovascular risk stratification, underscoring the important role of SUA/Cr in CHD prevention [16]. Optical coherence tomography studies have recently shown that elevated SUA/Cr is associated with a 2.3-fold increase in the prevalence of thin-cap fibroatheromas and larger macrophage infiltration areas, consistent with a vulnerable plaque phenotype [17]. A 2025 prospective study further confirmed that each one-unit increase in SUA/Cr raised the carotid plaque score by 1.77, indicating its independent predictive value for systemic vascular disease [18].

3.3. Insulin resistance pathway

Insulin resistance is an important contributor to atherosclerosis; its severity correlates positively with the number of diseased coronary vessels and the Gensini score, acting as an independent risk factor for the extent of coronary lesions [19]. Physiological insulin concentrations exert cardiovascular protection via the phosphoinositide 3-kinase–protein kinase B (PI3K-AKT) pathway [20]. In endothelial cells, PI3K-AKT directly phosphorylates endothelial nitric oxide synthase at serine 1177 (eNOS-Ser1177), increasing NO synthesis, inducing vasodilation and inhibiting platelet adhesion and monocyte chemotaxis, thereby blocking the initiation of atherosclerosis.

In vascular smooth muscle cells (VSMCs), activated PI3K-AKT maintains the synthetic phenotype through two parallel mechanisms: ① phosphorylation and inactivation of glycogen synthase kinase-3 β (GSK-3 β), which relieves phosphorylation-ubiquitin degradation of β-catenin and cellular-Myc (c-Myc), increasing their protein stability and promoting conversion to the synthetic phenotype;

② phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2), which activates mechanistic target of rapamycin complex 1 (mTORC1), enhancing phosphorylation of p70 ribosomal S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), facilitating cap-dependent translation and ribosome biogenesis to support the protein demands of the synthetic phenotype. When this pathway is inhibited or micro-environmental signals decline, these phosphorylation events reverse: GSK-3β re-activates, β-catenin and c-Myc undergo phosphorylation-ubiquitin degradation, and their stability decreases; mTORC1 activity falls, p70S6K and 4E-BP1 are dephosphorylated, translation initiation is suppressed and protein synthesis slows. Consequently, VSMCs shift to a contractile phenotype, proliferation decelerates, collagen secretion diminishes, the collagen framework of the fibrous cap is preserved and plaque stability is consolidated [21][22][23].

SUA/Cr is strongly and independently associated with the risk of metabolic syndrome (including hyperglycaemia, hypertension and dyslipidaemia) and its components. Studies have confirmed a positive correlation between SUA and insulin resistance. SUA reduces both basal and glucose-stimulated insulin secretion in isolated rat islets, and in-vitro work shows that uric acid induces β-cell apoptosis and dysfunction via the NF-κB-iNOS-NO axis. High SUA also blocks insulin-stimulated phosphorylation of Akt and eNOS, decreasing NO synthesis and thereby promoting coronary atherosclerosis [24][25][26][27][28]. Creatinine (Cr) is a stable product of muscle metabolism and is used to correct SUA for influences such as

muscle mass and sex. The corrected parameter, SUA/Cr, better reflects the true uric acid burden and correlates more closely with insulin resistance than SUA alone, thus more accurately mirroring the relationship between insulin resistance and coronary artery disease.

3.4. RAAS pathway

The renin–angiotensin–aldosterone system (RAAS) is a central regulator of cardiovascular physiology. Angiotensin II (Ang II) is closely linked to CHD; excessive activation of the Ang II type 1 receptor triggers inflammatory responses and oxidative stress, increases ROS and reduces NO, leading to endothelial dysfunction and cellular proliferation [29]. Ang II also promotes neovascularisation and intra-plaque haemorrhage, key factors driving plaque progression and instability [30], as confirmed in murine models [31].

An elevated SUA/Cr ratio indicates increased net SUA production. SUA up-regulates angiotensinogen mRNA expression and induces oxidative stress in human umbilical vein endothelial cells, thereby activating local RAAS, accelerating Ang II generation and precipitating coronary artery lesions [32].

4. Modulating SUA/Cr to reduce CHD impact

Although elevated SUA/Cr is closely related to CHD onset and progression, intervention strategies must be carefully balanced. Moderate reduction of SUA/Cr may attenuate coronary lesions by improving endothelial function and slowing CHD evolution. However, large cohort studies adjusting for age, sex and renal function have shown that SUA/Cr $\leqslant 4$ is significantly associated with cardiovascular mortality, whereas a ratio $\geqslant 8$ carries a 2.8-fold higher death rate than a ratio $\leqslant 4$ [33]. These findings suggest that very low SUA/Cr may reflect malnutrition, chronic depletion or impaired antioxidant capacity and can worsen prognosis. In such cases, nutritional support rather than further uric-acid lowering should be considered.

5. Conclusions and perspectives

As a renal-function-normalised index of net SUA production, SUA/Cr has emerged from obscurity to become an important window on the “double-edged sword” of CHD prognosis. Elevated SUA/Cr participates in coronary lesion development through oxidative stress, inflammation, insulin resistance and RAAS activation, ultimately leading to CHD. Moderate lowering of SUA/Cr can slow atherosclerosis, stabilise plaques and reduce ischaemic events, whereas an excessively low ratio ($\leqslant 4$) increases mortality. Patients with hyperuricaemia and CHD should be monitored for SUA/Cr; those already at low values ($\leqslant 4$) require nutritional assessment and support rather than intensive urate reduction. The precise “safe window” for SUA/Cr awaits further definition, and future individualised targets combined with drug-nutrient interventions represent a new direction for CHD prevention and control.

Conflict of interest：The authors declare that they have no competing interests.

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