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Review

Uric acid and cardiovascular disease

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ABSTRACT

Uric acid (UA) is an end product of purine metabolism in humans and great apes. UA acts as an antioxidant and it accounts for 50% of the total antioxidant capacity of biological fluids in humans. When present in cytoplasm of the cells or in acidic/hydrophobic milieu in atherosclerotic plaques, UA converts into a pro-oxidant agent and promotes oxidative stress and through this mechanism participates in the pathophysiology of human disease including cardiovascular disease (CVD). Most epidemiological studies but not all of them suggested the existence of an association between elevated serum UA level and CVD, including coronary heart disease (CHD), stroke, congestive heart failure, arterial hypertension and atrial fibrillation as well as an increased risk for mortality due to CVD in general population and subjects with confirmed CHD. Evidence available also suggests an association between elevated UA and traditional cardiovascular risk factors, metabolic syndrome, insulin resistance, obesity, non-alcoholic fatty liver disease and chronic kidney disease. Experimental and clinical studies have evidenced several mechanisms through which elevated UA level exerts deleterious effects on cardiovascular health including increased oxidative stress, reduced availability of nitric oxide and endothelial dysfunction, promotion of local and systemic inflammation, vasoconstriction and proliferation of vascular smooth muscle cells, insulin resistance and metabolic dysregulation. Although the causality in the relationship between UA and CVD remains unproven, UA may be pathogenic and participate in the pathophysiology of CVD by serving as a bridging mechanism mediating (enabling) or potentiating the deleterious effects of cardiovascular risk factors on vascular tissue and myocardium.

1. A short historical perspective

Uric acid (UA; 7,9-hihydro-1H-purine-2,6,8(3H)-trione; empiric formula $C_5H_4N_4O_3$; molecular weight of 168.11 Da) is a heterocyclic organic compound and an end product of purine metabolism in humans and great apes. Historical records show that UA crystals were first described by Antoni van Leeuwenhoek in 1679 in gouty tophus and, 50 years later, by William Stukeley in a tophaceous joint, although the chemical composition of the crystals at that time was unknown [1]. UA was first isolated in 1776 from urinary calculi by Swedish chemist Karl Wilhelm Scheele [2] who named the isolated substance *lithic acid* (from the Greek *lithos* meaning *stone* or *rock*). In 1798 George Pearson [3] isolated UA from 200 urinary stones and suggested the name *ouric* or *uric oxide*. The first chemical structure of UA was proposed by Ludwig Medicus [4] in 1875. In 1897 the German chemist H. Emil Fischer [5,6] - the 1902 Noble laureate for Chemistry - performed for the first time chemical synthesis of UA proving the accuracy of Medicus' proposed structure. Sir Alfred Garrod [7] provided the first evidence that gout was associated with increased UA levels in blood and he was the first to describe a method for UA measurement in serum or urine, which probably represents the first chemical test ever undertaken [1].

The link between elevated UA level and cardiovascular disease (CVD) or arterial hypertension was suggested nearly 140 years ago by Frederick A. Mohamed [8], who addressing the Bright's disease and its symptoms, wrote in Lancet: "Yet another class of individuals fail through the arteries. These, I am inclined to think, are more especially the gouty and syphilitic ones. Atheroma is their great enemy; it may attack their aorta or large vessels so badly that they get aneurism, and fall victims to this disease." Ten years later, in 1889, Haig and Oxon [9] wrote in British Medical Journal, "…that, caeteris paribus [other things equal], arterial tension varies with the amount of uric acid that is circulating in the blood." In 1951, Gertler et al. [10] found higher UA levels in patients with premature coronary heart disease (CHD) compared with normal population and suggested for the first time to consider UA as a potential risk factor for CHD. In the same year UA was included in the protocols of the Framingham study to be investigated as a potential risk factor for CVD [11]. In 1967, a seminal publication by Kannel et al. [12] reported the results of a 12-year follow-up of a large cohort (n = 5127 participants) in the setting of Framingham Study noting that elevated serum UA was associated with the risk of CHD in

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men 30–59 years of age, alongside elevated cholesterol. In the following years, the association between UA and CVD has been extensively investigated but the nature of the relationship between UA and CVD remains debatable. Difficulties in determining whether UA acts as a risk marker or a risk factor for CHD may be explained by its frequent association and intricate relationship with other cardiovascular risk factors, the possibility of reverse causation and conflicting findings from epidemiological or clinical studies undertaken to investigate the association of UA with atherosclerosis or CHD. A hypothesis that UA elevation may represent an adaptive change to protect from atherosclerosis due to its antioxidant properties has also been proposed [13]. The interest on UA has recently resurrected. The primary focus of this review is to summarize the current status of knowledge regarding the association of UA with CVD and discuss mechanisms of its involvement in the cardiovascular pathophysiology. Although, UA is intrinsically linked with xanthine oxidoreductase (XOR) enzyme, the association of this enzyme with CVD was not the focus of this review. This issue has been extensively reviewed [14–16]. Likewise CVD in the setting of gout was not addressed.

2. Basics of UA metabolism

UA, a weak organic acid with a pKa of 5.75 (diprotic acid with 2 dissociable protons with pKa_1 of 5.4 and pKa_2 of 10.3, respectively), is present principally (~99%) as monosodium urate at physiological pH values. Normal UA levels in serum are 2.6–5.7 mg/dl (155–339 μmol/L) in premenopausal women and 3.5–7.0 mg/dl (208–416 μmol/L) in men and postmenopausal women [17–19]. Solubility of UA in water is low and the UA concentration in blood close to solubility limit is 6.8 mg/dl. The total body pool of exchangeable UA is estimated to be ~600 mg in adult women and up to ~1200 mg in men. However, it may increase up to values ranging from 18,000 mg to 30,000 mg in patients with gout [20].

The basics of UA metabolism is covered in Fig. 1. In humans, UA is an end-product of catabolism of purine nucleotides arising from endogenous (nucleic acids and internal pool of purine nucleotides, mostly adenosine triphosphate [ATP], or their derivatives) and exogenous (dietary purines) sources. At the stage of monophosphate esters, nucleotidase enzymes act on adenosine monophosphate (AMP) and guanosine monophosphate (GMP), remove phosphate moiety and produce, adenosine and guanosine, respectively. Adenosine and guanosine products are further degraded via distinct pathways to produce hypoxanthine and xanthine, respectively. Hypoxanthine is further oxidized by xanthine dehydrogenase/oxidase to form xanthine which is further oxidized by the same enzyme to form UA as a final product of purine catabolism in humans and great apes [21]. In most other mammals, such as rats and mice, UA is further degraded by enzyme uricase to produce allantoin [22], which is 100 times more water-soluble than UA and consequently has more efficient urinary excretion route than UA [19,23]. However, in humans and higher primates, purine catabolism is stopped at UA stage due to the lack of functional uricase gene and consequently active uricase enzyme (see below). Mammals that have a functional uricase enzyme, typically display UA levels in the 1–2 mg/dl range, whereas humans and great apes have 3 to 10 times higher UA levels at least partly explainable by loss of functional uricase gene in the early Miocene era [24,25]. Although, XOR activity is detected in many tissues almost throughout the body [26–28], endogenous UA synthesis occurs mostly in liver, intestines, muscle including myocardium, kidney, mammary gland, corneal epithelium and vascular endothelium [29]. Exogenous purine pool varies with diet. Animal products such as red meat (particularly liver, kidney and sweetbreads), fatty poultry, high-fat dairy, seafood products and alcohol (particularly beer from the yeast) have high amounts of purines [23,30]. Increased cell turnover in the setting of many pathological processes (hemolysis, tumor growth or large tumor lysis syndrome) may increase the breakdown of nucleic acids leading to production of large amounts of purines which, in turn, increases the demand for purine elimination via UA production. Coffee and vitamin C may reduce this demand [31].

Although purine degradation pathway involves many enzymes [21], XOR is a critical and rate-limiting or house-keeping enzyme in purine metabolism. XOR, isolated first from bovine milk by Schardinger [32] as aldehyde reductase in 1902, is found across a wide range of species from prokaryotes to plants and animals. XOR has a relatively wide specificity and can oxidize a variety of endogenous or exogenous compounds including aldehydes, purines (like adenine, 6-mercaptopurine), a number of pyrimidines, pterines, azopurines, hetorocyclic compounds and various xenobiotics including antiviral and antineoplastic drugs and allopurinol [15]. Purified human XOR is a dimer of two identical subunits of ~150 kDa. Each subunit consists of three domains: a N-terminal 20 kDa, a middle 40-kDa and a C-terminal 85 kDa domen. The 1st, 2nd and the 3rd domains contain 2 non-identical Fe-S centers, a flavine adenine dinucleotide (FAD) cofactor and a 1 molybdopterin (Mo-pt) cofactor, respectively. Catalysis involves the sequential transfer of 2 electrons to the molybdenum atom (IV), Fe-S centers and FAD which is subsequently oxidized by molecular oxygen or nicotinamide adenine dinucleotide (NAD^+) [21,33,34]. In mammals, XOR is present in 2 interconvertible forms: xanthine dehydrogenase (XDH) which prefers NAD^+ and XOR which prefers molecular oxygen as acceptor of electrons. XOR reaction is associated with production of large amounts of highly cytotoxic oxygen reactive species (ROS), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). XOR is constitutively expressed as XDH which is converted (reversibly) to XOR through oxidation of sulfhydryl groups (to form -S-S- bridges) or limited proteolysis (irreversibly) [33]. Conversion from XHD to XOR is favored by reduced O2 tension and lower pH, tissue hypoxia or ischemia, ischemia/reperfusion cycle, glutathione depletion and presence of oxidizing agents such as hydrogen peroxide [15,35,36]. XOR is one of the most important ROS producers. ROS are important mediators participating in a wide range of cellular processes from cellular signaling (physiological role), to inflammation, aging, cancer, diabetes and CVD (pathophysiological role). Allopurinol inhibits XOR after being oxidized by the enzyme to oxypurinol which binds tightly to the molybdenum center. It has been suggested that in the presence of low NAD^+ concentrations, XDH may reduce (transfer electrons to) oxygen and produce ROS [21]. The human gene for XOR is located on the short arm of chromosome 22 (2p22) and contains 36 exons and 35 introns spanning at least 60 kb corresponding to a 1333 amino acid residue polypeptide [37]. Highest activity of XOR has been detected in liver, intestine and vascular endothelium whereas other human organs show a very low activity of the enzyme [21]. Of note, circulating XOR can bind to the surface of endothelial cells through glucosaminoglycans leading to increased oxidative stress and endothelial dysfunction [38]. This may explain “metastatic” damage by the activated enzyme in organs or tissues remote from the primary activation site. The expression of XOR gene in humans is lower compared with other mammals potentially due to promoter suppression [39] and is strict under regulatory control at transcriptional and post-transcriptional level (recently reviewed in [16]). The enzyme can be inhibited pharmacologically by drugs like allopurinol and febuxostat [40,41].

Since UA does not move freely across the cellular membranes, specific transporters enable UA transport across plasma membranes and play a crucial role in UA homeostasis. Although UA transporters have been detected in many types of cells, kidney and intestine harbor a large number of them consistent with their role as UA excretion routes. About 70% of UA is excreted by kidneys and the remaining 30% by gastrointestinal tract [42]. Kidney plays a crucial role in maintaining plasma UA levels and UA homeostasis in general, through complex and incompletely understood molecular mechanisms. A series of transmembrane proteins in epithelial cells serve as UA transporters enabling a balanced UA secretion/re-absorption. It should be noted that virtually all circulating UA is filtered in glomerulus and 90–95% of filtered UA load is re-absorbed, mostly in proximal tubules with the remaining

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