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Serum Uric Acid as Cardiovascular Disease Marker: Premises and Promises

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Abstract: Uric Acid (UA) is the final product of the activity of xanthine oxidase (XO) in the purine metabolism. The enzyme, XO linked to oxidative stress, endothelial dysfunction and heart failure in humans. Clinically, an association of hyperuricemia with hypertension, diabetes, renal disease and cardiovascular disease (CVD) has been observed over the years. With the increasing prevalence of obesity and diabetes worldwide, co-existing hyperuricemia is getting more focused attention than ever before. Despite its proposed protective role against aging and oxidative stress, epidemiological studies revealed an association between altered levels of serum uric acid (SUA) and various multi-factorial disorders such as hypertension, gout, dyslipidemia, obesity, glucose intolerance, insulin resistance and renal disease etc. Therefore, manipulation of SUA levels is now either included in, or being investigated for, the treatment of CVD including stroke. The role of SUA as an independent risk factor for myocardial infarction (MI) and cerebrovascular ischemic stroke (CVIS) has been previously discussed, though this association has been under keen observation in view of conflicting reports. Here we discuss the recent progress in our understanding about the clinical conditions which are related to SUA in MI and CVIS diseases. Also we describe here the possible involvement of SUA in monitoring, prognosis and therapy of these diseases which is not delved so far.

Keywords: Uric acid, cardiovascular disease, myocardial infarction and cerebrovascular ischemic stroke

Introduction

(1). Historic Background of Uric acid (UA)

Uric acid (7, 9-dihydro-1H-purine-2, 6, 8 (3H)-trione) was first isolated from urinary calculi by Swedish pharmacist and named the substance lithic acid [1]. Later it was named as uric acid (UA) [2]. UA is a heterocyclic compound of carbon(C), nitrogen (N_2), oxygen (O_2) and hydrogen (H_2) with the molecular formula of $C_5H_4N_4O_3$ (168.11 g/mol) (Fig-1). UA is a weak organic acid distributed throughout the extra cellular fluid as monosodium urate at physiological pH and is found as microscopic crystals in diseases (eg: gout) associated with elevated UA levels. UA has low water solubility and is negligibly soluble in all organic solvents.

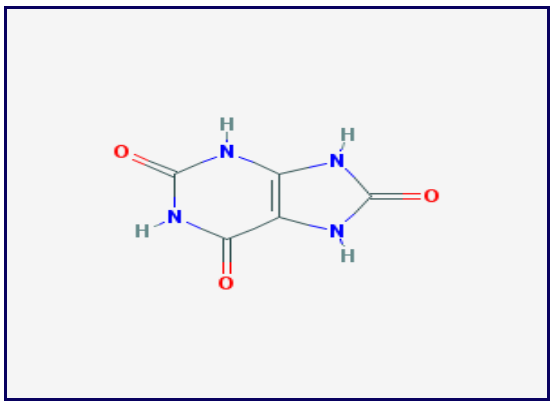

Fig-1: Structure of Uric acid (UA). UA is a heterocyclic compound of carbon (C), nitrogen (N), oxygen (O), and hydrogen (H) with the formula C5H4N4O3

(2). Bio-synthesis of Uric Acid (UA)

UA is the final breakdown product of purines, the principal constituent of adenosine triphosphate, DNA, and RNA, and its synthesis is mediated by the enzyme xanthine oxidase (XO). Nearly 15 million years ago, one of our hominid ancestors acquired a mutation in the gene for uricase, the hepatic enzyme that degrades UA into allantoin and other degradation products. As a consequence, having lost the ability to express urate oxidase, humans are exposed to higher UA (range 3-5 mg/dL) than other mammals. UA is formed in the liver and is the breakdown product of ingested and endogenously synthesized purine nucleotides, which are then oxidized by XO to UA and xanthine. The concentration of UA is determined by the balance between purine intake and UA production on one hand and UA elimination by the kidney and extra renal routes on the other [3]. Renal excretion is the major regulator of UA, decrease or increase in renal clearance is readily reflected by inverse changes in UA levels. These levels also were regulated by a four-component renal transport system involving glomerular filtration, reabsorption, secretion and post-secretory reabsorption [4]. Besides these, a number of kidney transporters are involved in

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the regulation of UA levels in the blood. In the kidney, it is filtered and can be subsequently reabsorbed or further excreted in the proximal tubule, predominantly under the action of a urate transporter-1 (URAT1), which is responsible for the reabsorption of UA. Next to the kidney, gastro-intestinal tract (GIT) is the major organ that helps in the excretion of ~30% UA, where it is degraded by uricolytic bacteria to carbon dioxide (CO_2) and ammonia (NH_3). In humans, approximately 90% of the filtered UA is reabsorbed [5].

(3). Hyperuricemia and metabolic risk factors

Since hyperuricemia was first described as being associated with hyperglycemia and hypertension by Kylin in 1923 [6], there has been a growing interest in the association between elevated UA and other metabolic abnormalities such as hyperglycemia, abdominal obesity, dyslipidemia, and hypertension [7].

The prevalence of hyperuricemia varies markedly depending on the difference in ethnic groups, geographic regions and survey years. Based on physicochemical, epidemiologic and disease-related criteria, a range of UA levels has been defined for both hyperuricemia and hypouricemia. Normal serum uric acid (SUA) levels are < 5 mg/dL in men and <4 mg/dL in women [8]. Hyperuricemia is the concentration of UA in the blood that exceeds the solubility limits of monosodium urate in plasma (>6.8 mg/dL). Above this concentration, SUA crystallization is induced in the joints. The higher the SUA levels, the more likely an individual is to develop gout [9]. SUA levels also increase with age [10]. SUA concentration is lower in premenopausal women because estrogen is uricosuric. After menopause, SUA levels in women are similar to men [11]. It is interesting to note that SUA levels may vary in the same individual during the course of a day, due to the effects of diet and exercise [9]. In one study, hyperuricemia has been defined for men as a SUA concentration >5.0 mg/dL [8]. For women, most studies define hyperuricemia as a concentration >3.0 mg/dL [8,12]. Whereas hypouricemia is defined as UA concentration in blood <2.20 mg/dL [13]. (Maxwell et al. [14] have reported that man had a significantly higher SUA than women (4.5 ± 1.3 mg/dL Vs 3.2 ± 1.4 mg/ dL). Therefore, the normal range of SUA levels falls somewhere between 3-5 mg/dL).

The major confounding factor for the change in SUA is diet. The amount of UA in the blood depends on the dietary intake of purines, UA bio-synthesis and rate of its excretion. If a person takes a diet rich in nucleoproteins (meat, particularly glandular meat, meat extracts, legumes) he/she will excrete excess of UA. Daily excretion of UA in a healthy person (which vary depending on age, sex and race) on a normal diet is about 700-1000 mg / day [15]. UA is constantly excreted in urine amounting to ~200-500 mg/day. However, the relationship between diet and SUA levels has not been fully established, since most studies do not correctly evaluate ingested nutrients [16].

Hyperuricemia can also result from a number of other factors like the intake of large amounts of alcohol, reduction in the glomerular filtration rate or decrease in the excretion of UA or an increase in overall tubular absorption [3-5,17]. Besides these, a number of diseases such as the myeloproliferative and lymphoproliferative disorders, tumor lysis syndrome (a complication of cancer chemotherapy), multiple myeloma, secondary polycythemia, pernicious anaemia, certain hemoglobinopathies, thalasemia, other hemolytic anemia's, infectious mononucleosis, Lesch-Nyhan syndrome (deficiency of hypoxanthine guanine phosphoribosyl transferase-HGPT) and glucose-6-phosphatase deficiency (Type I glycogen storage disorder) also results in secondary hyperuricemia due to elevated *de novo* purine biosynthesis [8]. In addition to these, hyperuricemia has been shown to be linked to a number of other metabolic disorders, which includes gout, hypertension, renal disease, cardiovascular disease (CVD), myocardial infarction (MI), cerebrovascular ischemic stroke (CVIS), insulin resistance (IR), obesity and dyslipidaemia [2,7,11,18]. These variable factors influence blood UA levels as they are associated with each other [19], what makes difficult to know which component can influence the blood UA levels [20]. However, it remains unclear whether an increased SUA level is the cause or a consequence of some of the conditions discussed below.

(a). Gout

Garrod in 1848 published the first account of the relationship between gout and levels of UA in the blood [21]. Gout is a complex metabolic disorder associated with an over production of UA. Gout rarely appears before 20 to 30 years of hyperuricemia. In the general population the prevalence of hyperuricemia ranges between 2.0 and 13.2%, and the prevalence of gout is between 1.3 and 3.7%, mostly affecting males. Post-menopausal women are however, as susceptible as men for this disease [11]. In acute hyperuricemia microcrystals of monosodium urate (MSU) get deposited in the soft tissues particularly in the joints and most often in the big toe. Such deposits are commonly called tophi, which causes severe pain and inflammation in the joints known as gouty arthritis. MSU can also precipitate in the kidneys and ureters that lead in stone formation and kidney damage. Obesity and heavy alcohol consumption also predisposes to attacks of gouty arthritis. Hyperuricemia does not

necessarily lead to gouty arthritis.

Based on the presence or absence of an identified cause of hyperuricemia, gout has been divided into two types, primary and secondary. Primary gout is more common without identifiable underlying cause for hyperuricemia. It has been reported that primary gout is an inborn error of metabolism leading to over production of purine nucleotides [22]. Many factors contribute to the conversion of asymptomatic hyperuricemia into primary gout such as age of the individual and duration of the hyperuricemia. Secondary gout is due to increased synthesis or decreased excretion of UA. Certain drugs (eg: thiazides) predispose to the development of secondary gout.

(b). Hypertension

Hyperuricemia predicts the development of hypertension in general population and emerged as a key independent risk factor for hypertension [23]. Several clinical, epidemiological and observational studies demonstrated a close association between SUA and hypertension, which is independent of obesity, renal function or anti-hypertensive medications [24]. It has been shown that ~25% of hypertensive individuals have hyperuricemia and this number increases to 75% in those with malignant hypertension [8]. Univariate associations of hyperuricemia with both systolic and diastolic blood pressure (BP) had been reported, but these relationships were attenuated after adjustment for Body Mass Index (BMI), suggested the role of adiposity in this association [25]. These observations are well supported by animal experiments, which shed light on a causal role for hyperuricemia in hypertension. For example, hyperuricemia was induced in Sprague-Dawley rats by uricase inhibitor, oxonic acid and these rats developed elevated BP at three weeks post treatment as compared to the control rats, which retained normal BP [26,27]. The induced elevation in BP in experimental rats was reversed by the administration of an angiotensin converting enzyme inhibitor, enalapril [26].

(c). Obesity

Obesity has reached epidemic proportions in the past two decades and represents one of the most important components of the metabolic syndrome and a major risk factor for type-2 diabetes [28]. The association of hyperuricemia with obesity and increasing BMI was found in American Indians [28], Europeans [29], Japanese [30] and Marian Island population [31]. In obese subjects, hyperuricemia is attributable to the over production of UA or impairment in the renal clearance of UA owing to the influence of hyper-insulinemia, secondary to insulin resistance (IR) [30] .Weight reduction is correlated with a modest lowering of SUA levels and a decrease in the rate of *de novo* purine synthesis [32].

A positive link between SUA and serum leptin (a hormonal product of the obese gene) levels has been reported in healthy male adolescents [33] and in moderately obese women [34]. Most obese people showed resistance to leptin and elevated SUA levels were significantly correlated with IR among non-diabetic individuals [35]. In contrast, Matsubara et al. [36] observed an independent association between serum leptin and SUA levels among Japanese women and children, even after adjusting for BMI and body fat. These studies imply that association of SUA, obesity and IR may at least in part, be mediated by leptin expression.

(d). Diabetes

Several studies have reported the association of SUA with the incident of type-2 diabetes but these studies were conducted on male population. In early prospective studies, it has been demonstrated that for 1 mg/dL increase in baseline SUA levels, a 1.14-fold increase in diabetes risk during a 5-year follow-up in middle-aged Israeli men [37]. Among the randomized study in Swedish men, the multivariate adjusted risk for the development of diabetes during a 13.5-year follow-up was reported as 5.8 fold for those in high value [38].

Monica Augsburg Cohort Study is the first population-based prospective study in women that explored the prediction of SUA for the development of diabetes in Germany [39]. The Rotterdam study, a prospective cohort of individuals aged 55 years and above showed 1.68 times higher risk of developing type-2 diabetes in the top quartile of UA (> 6.2 mg/dL) than lowest quartile of UA (<4.5 mg/dL) [40] . Another study in the Chinese population of Taiwan revealed that high SUA levels at baseline examination independently predicted the development of type-2 diabetes in women with an odds ratio of 1.44, but not in men [41]. Similar to these observations, Chien and colleagues [42] have shown that baseline SUA is an independent predictor of future type-2 diabetes incidence in a community-based prospective cohort study of Chinese participants in Chin-Shan town, Taiwan.

(e). Dyslipidemia

An association between hyper-triglyceridemia (HTG) and hyperuricemia is well established in way back 1968 by Barlow [22]. Up to 80 % of individuals with HTG have hyperuricemia and 50 to 75% of gouty patients have HTG. Obesity and excessive alcohol intake are the confounders of the link between HTG and hyperuricemia. Free fatty acids have also been shown to be related to hyperuricemia independently

of HTG, obesity and body fat distribution [43]. Elevated levels of serum apolipoproteins (A-II, B, C-II, C- III, and E) with decreased HDL cholesterol in patients with hyperuricemia has been reported [20]. Though the prevalence of apolipoprotein-E2 allele was shown to be greater in hyperuricemia patients and is associated with higher triglyceride levels [44], but the potential mechanism relating hyperuricemia to fasting HTG is not known. It has been speculated that it may be due to an increase in nicotinamide adenine dinucleotide phosphate oxidase (NADPH) requirement for *de novo* fatty acid synthesis in obese subjects [45].

(f). Myocardial Infarction (MI)

Atherosclerosis leading to myocardial infarction (MI) is the most common and severe clinical manifestation observed in cardiovascular diseases (CVD). MI usually results from the rupture of the atherosclerotic plaque with thrombus formation and occlusion of the coronary vessel, causing in an acute reduction of blood supply to a portion of the myocardium. The average age for acute MI (AMI) attack in Indians has decreased by 20 years and about half of the reported MI cases are below the age of 50 [46].

Despite considerable improvements in prophylaxis and treatment, MI remains a common life threatening disease [47]. Worldwide, of the 17.5 million deaths due to cardiovascular diseases, 20% deaths occurred in high income countries, 8% in upper-middle income countries, 37% in lower-middle income countries and 35% in low income countries including India [48]. Recent case-control studies in India have reported that being illiterate or poor is an independent risk factor for Acute Myocardial Infarction (AMI). It has been estimated that India had the highest number of deaths (over 1.5 million) in the world due to CAD in 2002, which is expected to double by 2015 [48]. Many of the standard coronary risk factors such as smoking and tobacco use, low physical activity, high dietary fat intake, uncontrolled hypertension, uncontrolled hypercholesterolemia and diabetes are also more common among the low socioeconomic individuals [49,50].

A positive association between SUA and MI has been recognized for little over 60 years [51]. It has been shown that elevated SUA levels associated with increased cardiovascular morbidity and mortality [9, 52, 53]. Johnson and colleagues have shown that hyperuricemia predicted the development of MI in individuals not only with hypertension but also in the general population [8]. Similar results have been reported in a population-based cohort study of a 12-year follow-up in middle-aged healthy Finnish men [54].

Different prospective studies exploring the inter-relationship between SUA and cardiovascular outcomes in various categories of subjects are summarized by Strazzullo and Puig [55]. The first large prospective study was done in Austrian men cohort who was prospectively followed for a median of 13.6 years [56]. This study confirmed the independent relationship between elevated SUA and mortality from MI, but the association of SUA with mortality from acute, sub-acute, or chronic forms of MI after adjustment for potential confounding factors was not present. In another study of 1,017 patients with angiographically proven MI has been shown a 5-fold increase in overall mortality rates with elevated SUA levels as compared to the controls [57]. Recent study by Eisen et al. [58] suggested that SUA levels are associated with future risk of heart failure in patients with stable MI, but this association is attenuated after adjusting for traditional MI risk factor.

The Framingham study with 6,763 subjects whose baseline SUA levels were tested from 1971 to 1976, supported the contention that traditional risk factors, rather than hyperuricemia, are the primary casual factors in the development of atherosclerotic heart disease during follow-up [59]. In this study, hyperuricemia was not associated with an increased risk for adverse outcomes like MI, death from MI, or death from all causes after adjustment for other cardiovascular risk factors in men and women [58]. A recent study from NdrePepa et al.[60] showed that elevated levels of SUA is an independent predictor of 1-year mortality in all spectrum of acute coronary syndrome patients treated with percutaneous coronary intervention, thus strengthening the prognostic value of SUA, not only for short term, but also for a longer follow up period.

The issue of hyperuricemia as an independent risk factor for atherosclerotic-MI has received much renewed interest in recent years with many reviews and editorials providing different views [61-63].The association of high SUA levels with MI may be due to the role of UA as an antioxidant, because an elevated SUA may be a defense mechanism against atherosclerosis [64]. SUA levels may increase in an attempt to block lipid peroxidation [65]. There is some evidence that, SUA could possibly promote, rather than prevent, oxygenation of low-density lipoprotein, cholesterol and lipid peroxidation [66]. High SUA levels can also stimulate the release of free radicals, which have been shown to alter the expression of cell adhesion molecules (eg: integrins) and cell surface receptors (eg: Toll like receptors) in cardiac cells resulting endothelium damage thereby risk of developing MI [2]. However, studies are necessary to understand the actual role of hyperuricemia in this scenario and whether it can truly be of any value in the early identification of

individuals at risk of developing MI.

For early detection of MI, simple and specific cardiac biomarkers are being developed, though none is available currently over the counter (OTC). The serum C-reactive protein (C-RP) appears to be a reliable biomarker for early detection of MI [67]. Skeletal muscle synthesizes creatine kinase (CK) and MI cause significant elevation about 20 hrs after the onset of coronary occlusion. It measures the blood levels of two variants i.e isoenzymes CK-MB (creatine kinase muscle) and creatine kinase brain (CK-MB) of the enzyme phosphocreatine kinase. Though CK-MB appears to be the sensitive method for the diagnosis of an MI, the complex protocol combined with low specificity has led to CK-MB a non-reliable biomarker [68]. Therefore, there is a need to find simple and reliable and cost effective prognostic markers particularly for rural areas in developing countries where fibrinolytic treatment is still the first choice of acute reperfusion therapy due to non-availability of simple diagnostic methods.

Contradictory to the above studies, several reported have shown that SUA is the negative prognostic indicator in patients with AMI, due to several confounding variables such as age, obesity, diabetes, alcohol consumption and use of diuretics have made it difficult, to date, to indisputably establish the role of SUA as an independent risk factor for MI [69,70]. Based on the results of a meta-analysis from 15 prospective studies, Wheeler et al. [71] have reported that SUA levels neither predict the MI nor determinant of the disease in general populations.

(g). Cerebrovascular Ischemic Stroke (CVIS)

Cerebrovascular Ischemic Stroke (CVIS) is a high socio-economic burden with dire consequences for the patient and for society and will increase in prevalence over the coming years [72]. CVIS is defined by the World Health Organization (WHO) as a syndrome of "rapidly developing clinical symptoms of focal disturbance of cerebral function lasting more than 24 hrs. CVIS involves blood vessels in the brain. According to the American Stroke Association's website, "A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot (ischemic stroke) or bursts (hemorrhagic stroke). About 87% strokes are ischemic. When that happens, part of the brain cannot get the blood (and oxygen) it needs, so it starts to die. Every minute that a stroke goes untreated, almost two million brain cells die. That is 14 billion synapses and 7.5 miles of myelinated fibers gone every minute. Treatment within 60 minutes of the first symptoms often leads to a good prognosis. The longer the stroke lasts, the greater the damage to the brain thereby increase infarct volume [73].

Hemorrhagic strokes account for 13% of all strokes, yet are responsible for more than 30 % of all stroke deaths. Annually worldwide 10.5 Million people suffer a stroke. 5 million die and 5 Million are permanently disabled [74]. Approximately 55,000 more women than men have a stroke each year. Stroke can happen to anyone at any time, regardless of race, sex or age. It is of interest that those who have suffered stroke have a higher risk of recurrent stroke than of myocardial infarction (MI), whereas the opposite applies for those who have suffered MI. A family history of heart disease increases stroke risk, as does being over the age of 55 yrs. WHO estimates that a stroke occurs every 5 seconds [75], and stroke related deaths are the 6th most common cause of deaths and accounts 9.6 % of all deaths in the world. Two-thirds of these deaths occurred in people living in developing countries and 40% of the subjects were aged less than 70 years. Additionally, CVIS is the leading cause of disability in adults and each year millions of stroke survivors has to adapt to a life with restrictions in activities of daily living as a consequence of CVIS. Many surviving CVIS patients will often depend on other people's continuous support to survive.

In India, CVIS prevalence is 55.60% per every ten lakh people at all ages [61]. Prevalence of stroke in rural or in urban India was estimated to be in a range of 84-262 and 334-424 cases respectively per every ten lakh people. Approximately, 1.44 to 1.64 million cases of new acute strokes occur in India every Year [61]. Nearly 12.0% of strokes occur in the population aged <40% [76]. Some of the major risk factors known to cause CVIS are smoking, high blood pressure, obesity, high cholesterol and high triglycerides etc. Approximately 25% of strokes are recurrent events and approximately 25% of stroke patients will suffer recurrence within 5 years [77]. The risk of recurrence may be highest early, with approximately 4% suffering recurrence within one month and 12% at one year [78] .

CVIS outcome is generally influenced by stroke severity, age of the patient, quality of care received and presence of several confounding variables such as obesity, alcohol consumption, age, quality of care received and diabetes have made it difficult, to date, to link SUA with CVIS [79-81] reported the association between SUA and triglyceride levels. In a landmark study, improved cardiovascular end points were attributed to the hypouricemic effect of Losartan ahead of its hypotensive effect, a finding that somewhat divested elevated SUA from blood pressure in CVIS [82]. It is not completely clear whether this association indicates SUA is an independent CVIS risk factor. Whether the concentration of SUA at the onset of ischemic symptoms influences the severity of stroke also

remains to be explored. Moreover, the allegedly greater risk of stroke or death attributable to hyperuricemia in some studies challenges the antioxidant properties shown by this molecule. The practical application of this conclusion deserves some thought.

Stroke is associated with an increase of reactive oxygen species (ROS) and compensatory increase of anti-oxidant activity. SUA becomes pro-oxidant at high concentrations. ROS contribute to the cerebral and cardiac sympatovagal imbalance and are arrhythmogenic. The increase of UA could be a protective mechanism in stroke patients up to a point, and the absence of fatal events could be due to this increase. Elevated SUA becomes a negative prognosis factor, due to its pro-oxidant effect [83]. SUA could therefore serve potentially as a surrogate marker of oxidative stress and an add-on therapy in acute ischemic stroke [84].

The other mechanisms in which SUA causes injury to the cardiovascular system includes its effects on the endovascular endothelium, increases in platelet aggregation, alteration in hemorrheology and inhibition of the synthesis of nitric oxide [85]. Although, SUA an easy detectable serum marker, is a marker of adverse outcome and sudden cardiac death in stroke patients, but till date the available results suggests the association between SUA levels and CVIS outcome remains debatable. Because, some reports have indicated that elevated SUA with poorer outcomes in acute strokes, while, others have found different results [86].

(h). Stroke Prevention Strategies

Despite the clear and significant burden of acute stroke, there are depressingly few effective treatments. The only proven effective interventions are stroke unit care, aspirin and reperfusion therapy with intravenous thrombolytic therapy and intra-arterial thrombolysis in a small subset of patients with proximal middle cerebral artery occlusion. The link between serum cholesterol levels and coronary artery disease is well established and the evidence that cholesterol lowering therapy with HMG-CoA reductase inhibitors (statins) reduces coronary morbidity and mortality in those with established stroke. Thus, statin therapy is clearly indicated and recommended as a preventative strategy in those who have suffered ischemic stroke. Whether statins should be given to those who have suffered stroke and have no other indication for their use is at the time of writing unclear.

All patients with suspected acute stroke should undergo emergency brain imaging to help confirm the diagnosis, distinguish infarct from hemorrhage and to identify important differential diagnoses such as tumor. The choice of brain imaging modality lies between computed tomography (CT) and magnetic resonance imaging (MRI). An urgent brain scan enables rapid differentiation of ischemic from haemorrhagic stroke. Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is the only licensed treatment for acute ischemic stroke where it must be administered within 3 hrs of symptom onset**.** Trials are ongoing to assess efficacy of thrombolytic therapy in ischemic stroke up-to 6 hrs after the onset of symptoms and to establish whether newer imaging techniques can better guide thrombolytic therapy and perhaps allow treatment up to 9 hrs after onset in selected patients. Results of small phase-II studies of this later approach have been conflicting, although it remains a promising strategy. Neuroprotectant drugs aim to save ischemic brain tissue by damping down the potentially harmful molecular processes in the penumbra. Unfortunately, no neuroprotectant strategy has yet been proven effective in phase III clinical trials, although at the time of writing this review, several agents are the subject of clinical trials. Therefore, studies are necessary to understand the actual role SUA has in this scenario and whether they can actually be of value in the early prognosis of individuals at risk of developing CVIS.

(i). Methods for Reducing UA Levels in serum

Once thought to be a metabolically inert product of purine metabolism, UA is now being recognized as a potent antioxidant of which concentration in plasma is nearly 10 times higher than other antioxidants (vitamins C and E) and it accounts for a substantial part of the antioxidant property of plasma [87,88]. In humans, approximately one half the antioxidant capacity of plasma comes from UA [86]. Current evidence shows that UA is a potent antioxidant whose serum concentration increases rapidly after acute MI and CVIS [64,89] , but the prognostic significance of SUA in CVIS can best be described as controversial at present [74]. Various treatment strategies for reducing overall UA concentration have been developed. Initially, dietary and lifestyle changes are encouraged, as many of the causes of hyperuricemia are correctable and the use of drugs to lower UA levels is often life-long. These include decreasing the consumption of protein, purines, and alcohol, as well as reducing obesity. These dietary source of UA are impossible to regulate, but high-risk individuals with hyperuricemia might reasonably be advised to avoid purine-rich foods, such as liver, sweetbreads, kidneys, beef, pork, seafood, sardines, several other meats and fish, and some legumes. Not much left to satisfy the gourmet palate, but that may be the price some of us need to pay for better cardiovascular health.

(j). Caveates in the epidemiological evidence

There are two types of drugs that are used to treat chronic hyperuricemia. XO inhibitor, allopurinol that inhibit the production of UA by blocking the final two steps of UA synthesis. In spite of promising early data, allopurinol has failed to generate adequate scientific interest to conduct well-designed randomized controlled trials in high-risk population. A clinical trial to investigate the benefit of 2 years treatment with 300 mg allopurinol on changes in carotid intima-media thickness (IMT) was started in May 2009 with 500 cases of recent stroke patients. The hypothesis behind this trail was to see whether 300 mg dose of allopurinol will reduce IMT progression rate, increase the levels of EPCs and reduce the levels of circulating endothelial markers with no increase in serious adverse events. The study results would be expected to complete by the end of 2014. The second type of drugs for example, febuxostat, a novel non-purine selective inhibitor of XO appears exciting. However, there are no large scale clinical trials evaluating its benefit in improving survival in high-risk patients. Further, if the elevated SUA levels are caused by a low UA clearance, uricosuric drugs, such as probenecid, sulfinpyrazone and benzpromarone are used to reduce the UA concentration through the inhibition of the URAT1 transporter [17]. However, future clinical trials should be considered to address the effect of these drugs on BP, endothelial dysfunction, left ventricular hypertrophy and mortality in high-risk populations. What is lacking, however, is a good prospective study of UA lowering with hard endpoints, such as cardiovascular mortality. Until we have that, it would be premature to suggest adding drug-based UA lowering to the list of interventions for reducing cardiovascular risk.

(k).Future directions

It appears that UA is not an inert organic compound, as has historically been believed, but can instead play a role in many biological functions [90]. Studying the role of UA in the pathogenesis of AMI and CVI has been challenging, not least because of the nature of these diseases. Moreover, the relationship between UA and cardiovascular risk prognosis is ambiguous. Some studies have explored this relationship but have contradictory results. Several potential explanations have been put forward to explain the possible association between hyperuricaemia and MI and CVIS. Studies have demonstrated that mechanisms by which UA could be injurious to the endothelium and to cardiovascular function. Paradoxically, UA elevation could be expected to confer protective anti-oxidant effects in the cardiovascular system, but these potential benefits may be obscured by detrimental effects elsewhere. The effects of raising or lowering UA on endothelial function and progression of CVD require direct investigation, to understand a possible dual action in the cardiovascular system. Identifying the mechanisms by which UA interacts with cardiovascular regulation will give us greater understanding of the role of hyperuricaemia for individual patients and allow a more rational approach to treatments that modify SUA concentration.

Furthermore, several clinical trials if not all, we listed in this review are small and examined highly defined populations. For example, it is not known whether lowering UA levels with allopurinol will be effective in people with more severe or longstanding hypertension. Nor do we know whether the beneficial effect of allopurinol observed in completed and preliminary human studies is due to the reduction of UA or to a reduction in XO–associated oxidants. Moreover, allopurinol is not a benign drug, and may occasionally precipitate a hypersensitivity syndrome that can be fatal. It is also known that UA can also stimulate innate immunity through the effects of microcrystalline UA on the function of dendritic cells and T cells. Thus, it remains possible that UA may have a variety of as yet incompletely defined actions in CVD. Currently, there is no data to suggesting the treatment of symptomatic hyperuricemia. Further interventional studies may clarify whether therapies that lower SUA may benefit patients at high risk for CVD. Therefore, future research should focus on confirming the pathogenetic mechanisms of hyperuricemia and examine the role of urate lowering therapy in stroke. In conclusion, if the available results on SUA stand the test of time, one of the causes of cardiovascular risk events could be suggested and investigated.

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