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Review Article

Hyperuricemia and global Cardiovascular Risk: State of the art and preventive prospects

Abstract

Over the last years, scientific research has focused its interest on a potential role of hyperuricemia as cardiovascular risk factor; main interest has been directed to persistent raised plasma levels of uric acid. Although some studies have not shown a close correlation between hyperuricemia and cardiovascular risk, most scientific evidence agrees that hyperuricemia plays a key role in determining cardiovascular events and in development of other risk factors often associated with only moderately increased serum uric acid levels. Pathophysiological mechanism underlying this association mainly include a hyperuricemia-induced endothelial dysfunction, inflammatory and oxidative stress induced by high serum uric acid levels. Early diagnosis, follow-up and prevention programs and effective treatment of hyperuricemia are recommended in particular in patients with other concomitant cardiovascular risk factors. Urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 µmol/L) though in high risk patients the lowest possible value of uric acid is better.

Introduction

Cardiovascular risk is a cluster of factors including hypertension, diabetes, overweight/obesity, dyslipidemia, metabolic syndrome, tobacco use and others, which predispose and increase the risk of cardiovascular events, mainly cardiac ischemic disease and stroke [1]. Over the last years, scientific research has focused its interest on a potential role of hyperuricemia as cardiovascular risk factor; main interest has been directed to persistent raised plasma levels of uric acid [2].

Uric acid, an heterocyclic organic compound, is the final oxidation product of exogenous and endogenous purine metabolism and is excreted in urine. The endogenous production of uric acid is mainly from liver and intestines and represents the main amount of circulating uric acid, about 600-700 mg daily; diet and animal proteins contribute to exogenous purine pool, for about 100-200 mg daily. In human, the enzyme Xanthine oxido-reductase catalyzes two terminal reactions of purine catabolism, leading to formation of uric acid from xanthine and hypoxanthine, which in turn are produced from other purines, primarily adenine and guanine [3]. In the extracellular compartment, urate is largely present as monosodium urate, with a low solubility limit of about 6.8 mg/dL (404 µmol/L) [4]. Most of circulating uric acid is freely filtered in the kidney and roughly 90% of the filtered load is normally reabsorbed along the proximal tubules of nephrons. Renal excretion of uric acid represents approximately 60–70% of total uric acid excretion from the body; a smaller proportion of uric acid is secreted in the intestine, and is further metabolized by resident gut bacteria in a process termed intestinal uricolysis [5].

Asymptomatic hyperuricemia is common and usually does not progress to clinical Gout, a chronic inflammatory arthritis caused by a disorder of the purine metabolism leading to hyperuricemia. Possible complications of hyperuricemia are Acute uric acid nephropathy, Uric acid nephrolithiasis and Chronic urate nephropathy [6].

There is evidence that chronic increased uricemia seems to behave in a not dissimilar way to other traditional cardiovascular risk factors that are often associated with hyperuricemia in so close relationship to suggest the existence of a pathogenetic link [7]. Moreover, hyperuricemia is prevalent in subject with poor control of blood pressure values and in those with higher grade of obesity and lower HDL-cholesterol plasma levels [8].

Scientific evidences

In 1999, data from the Framingham Heart Study, that examined a possible relation of serum uric acid levels to cardiovascular disease, concluded that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes.

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Any apparent association with these outcomes were probably due to the association of uric acid levels with other risk factors [9]. However, one year later, results from the NHANES I study showed that increased uric acid levels had a positive relationship to cardiovascular mortality and were independently and significantly associated with the risk of cardiovascular mortality [10]. Afterwards, data from a prospective study and meta-analysis stated that serum uric acid levels is unlikely to enhance usefully the prediction of coronary artery disease and this humoral parameter is unlikely to be a major determinant of the disease in general populations [11]. More recently, two meta-analysis, have reported that hyperuricemia may lead to a modest increment in the risk of stroke incidence and mortality [12] and increases the risk of all-cause mortality and cardiovascular mortality [13].

On the other hand, beyond these conflicting results, it is undeniable that there is a lot of evidence that shows the link between high plasma levels of uric acid and cardiovascular risk. Animal [14-16], and clinical studies [17-20], have shown as hyperuricemia is associated with high blood pressure and with increased future risk of incident hypertension, independent of other risk factors; this risk appears more pronounced in younger individuals and women [21]. Elevated serum uric acid is also independently associated with left ventricular mass index [22]. Although a recent meta-analysis states that hyperuricemia may modestly increase the risk of hypertension incidence, consistent with a dose-response relationship [23], high plasma levels of uric acid were identified as independent predictive factors of hypertension development. A significant epidemiological correlation was also found between hyperuricemia, insulin resistance and other components of metabolic syndrome [19,24], moreover, serum uric acid levels are positively associated with the development of type 2 diabetes regardless of various study characteristics [25]. In patients with insulin-resistance the increase in serum urate has often been considered to be secondary; however, in a long-term prospective study high levels of serum uric acid were found to be a strong and independent predictor of incident metabolic syndrome [26]. Moreover, a recent metanalysis provided strong evidence that hyperuricemia is a risk factor for developing type 2 diabetes in middle-aged and older people, independent of other established risk factors, especially metabolic syndrome components [27]. Although these evidences suggest that hyperuricemia may play a pathophysiological role in glucose dysmetabolism, further research should attempt to determine whether it is effective to utilize uricemic plasma levels as a predictor of type 2 diabetes for its primary prevention [28]. It has been also found that serum uric acid concentration is associated with microalbuminuria, glycated hemoglobin and carotid intima-media thickness in type 2 diabetics [29,30]. In two recent italian longitudinal studies of a cohort of type 2 diabetics, mild hyperuricemia was found strongly associated with the risk of chronic kidney disease [31] and increased serum uric acid is found to be an independent predictor factor of this complication [32]. Randomized trials have also shown that reducing hyperuricemia by anti-hyperuricemic treatment leads to significant improvement in endothelial function [33,34], this effect has been observed in diabetic patients with [35] and without hypertension [36,37]. Moreover, long-term and high-dose therapy with the anti-hyperuricemic drug Allopurinol has allowed to achieve significant improvement in glycated hemoglobin values in type 2 diabetic patients [36]. These data might well hypothesize a role of hyperuricemia even in the determinism of vascular complications of diabetes.

In addition, correlations were found between hyperuricemia and microvascular damage in kidney and it has been shown that hyperuricemia is also an independent risk factor for the development of chronic renal dysfunction in general population [38,39], in patients with hypertension [40] and in diabetics [32,41].

Potential pathogenetic mechanisms

Pathophysiological mechanisms underlying the association between hyperuricemia and cardiovascular risk mainly include a hyperuricemia-induced endothelial dysfunction. The main determinants of vascular damage are the activation of the renin–angiotensin–aldosterone system and the production of reactive oxygen species resulting in cytokines production and in reduced endothelial bioavailability of nitric oxide. Uric acid has pro-inflammatory activity by stimulating the production of Interleukin-1beta, Interleukin-6, Tumor necrosis factor-alfa and other cytokines [42,43]. Another possible pathogenetic mechanism that can explain the vascular damage uric acid-related is the hyperactivity of the enzyme Xanthine oxido-reductase observed in hyperuricemic patients. Xanthine oxido-reductase catalyzes the last two steps of purine catabolism, the oxidation of hypoxanthine to xanthine and the oxidation of xanthine to uric acid. This enzyme exists in two forms: Xanthine dehydrogenase, which prefers NAD+ as electrons acceptor, and Xanthine oxidase, which generates electrons that are transferred directly to molecular oxygen; as a result of these reactions are produced two reactive oxygen species, superoxide anion and hydrogen peroxide, that contribute to amplify the oxidative stress and endothelial dysfunction [44,45].

In summary, hyperuricemia negatively affect vascular function by exerting pro-oxidant effects and by decreasing nitric oxide bioavailability, thus inducing inflammation and endothelial dysfunction, which may promote hypertension, diabetes, metabolic syndrome, nephropathy and cardiovascular disease.

Anti-hyperuricemic treatment and serum uratic target

There is no universally accepted definition of hyperuricemia. A physiochemical definition of hyperuricemia, based upon the solubility limit of urate in body fluids is widely preferred over a statistical definition because of the non-normal distribution of serum urate concentrations in most populations. This physicochemical definition corresponds to urate concentrations exceeding about 6.8-7 mg/dL (404- 416 µmol/L), as measured by automated enzymatic (uricase) methods in routine clinical laboratory use; these values are approximately 1 mg/dL (60 µmol/L) lower than those obtained with colorimetric methods [6,46].

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Therapeutic approach of hyperuricemia, and its prevention, include lifestyle and dietary recommendations. Since high uric acid levels are often associated with metabolic syndrome, weight reduction with daily exercise should be encouraged to prevent hyperuricemia by reducing insulin resistance. Changes in eating habits and in nutritional style would help reduce uric acid levels; low intake of dietary purine as red meat, animal entrails, crustacean and high-purine vegetables, as asparagus, spinach, peas, cauliflower or mushrooms, is recommended. Heavy drinking, ethanol and high fructose corn syrup-sweetened sodas should be avoided; whereas moderate drinking, sweet fruits, and seafood intake, particularly oily fish, should be tailored to the individual, considering their anticipated health benefits against cardiovascular diseases. Dairy products, vegetables, nuts, legumes, fruits (less sugary ones), and whole grains are healthy choices for the comorbidities of hyperuricemia and may also help prevent it by reducing insulin resistance. Adequate hydration may be useful to maintain a high urine output of at least 2 L daily; supplement of potassium citrate and occasionally sodium bicarbonate may be required to alkalinize the urine and to increase the solubility of uric acid. Folate intake, vitamin C supplementation and coffee consumption seem associated with a lower risk of incident gout, while thiazide and loop diuretics can increase blood uric acid levels by interfering with renal clearance. [6,47,48].

Allopurinol, a competitive inhibitor of Xanthine oxido-reductase, is the most widely used anti-hyperuricemic agent, though not all patients are able to achieve a sufficient therapeutic response. Allopurinol can be used in almost any hyperuricemic state and the usual maintenance dose for adults is 200-300 mg once-daily; however a dose adjustment is required in patients with chronic renal failure because a higher incidence of adverse effects is observed if the dose is not adjusted. Allopurinol is well tolerated, but potential severe or fatal hypersensitivity reactions may develop; hepatotoxicity, bone marrow depression, and interstitial nephritis are rare but serious side effects of Allopurinol [49]. As well as being the most widely used anti-hyperuricemic, Allopurinol is also the most studied agent. Several studies have shown that anti-hyperuricemic treatment with Allopurinol has allowed to achieve a reduction in systolic and diastolic blood pressure values [50], regression of left ventricular mass in type 2 diabetic patients [51] and a prolonged exercise capability in patients with chronic stable angina [52]. It has also been shown that Allopurinol slows down the progression of renal failure in patients with chronic kidney disease [53]. At last, as already mentioned, Allopurinol allows to obtain a significant improvement in endothelial function [34-37], by reducing oxidative stress in the vasculature and improving endothelium-dependent dilation [54]. Another novel Xanthine oxido-reductase inhibitor, approved by the US Food and Drug Administration (FDA) in 2009 for long-term treatment of hyperuricemia in patients with gout, is Febuxostat [55]. In the CONFIRMS trial [56], a comparative study between Febuxostat and Allopurinol, Febuxostat 40 mg daily was statistically not inferior to Allopurinol 300 mg daily in lowering uric acid levels in patients with normal renal function, while Febuxostat 80 mg daily proved superior to both in such patients ($p < 0.001$); moreover, in patients with mild-to-moderate renal failure, Febuxostat at any dose was superior to Allopurinol in lowering uric acid levels and no dose adjustment was required in these patients. Although in the CONFIRMS study cardiovascular event rates were 0.0% for Febuxostat 40 mg and 0.4% for both Febuxostat 80 mg and Allopurinol 300 mg, some previous studies have identified cardiovascular events during Febuxostat treatment so that large ongoing trials are comparing the cardiovascular safety of Febuxostat versus Allopurinol [55]. In the FLORENCE study, a recent large adult trial carried out in tumor lysis sindrome prevention, Febuxostat at fixed dose of 120 mg daily has also achieved a significant superior serum uric acid control in comparison to Allopurinol, with comparable renal function preservation and safety profile [57].

Other novel anti-hyperuricemic agents are Rasburicase, Pegloticase and Lesinurad; Rasburicase [58], is a recombinant urate oxidase that facilitates the conversion of urate to a more soluble product, allantoin. It is approved, at a dose of 0.2 mg/kg daily as a 30-min infusion, in preventing complications of hyperuricemia for patients at high risk of tumor lysis syndrome [59]. Pegloticase is a recombinant, pegylated, uric acid–specific enzyme, administered by intravenous infusion that catalyzes the oxidation of uric acid to allantoin. It is approved for use in adults with chronic gout that is refractory to conventional therapy. During Phase-3 trials with Plegoticase were reported three cases of heart failure exacerbation and a case of nonfatal myocardial infarction; high cost and safety profile might limit its use in clinical practice [60]. Lesinurad is an oral selective uric acid reabsorption inhibitor approved by the FDA for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a Xanthine oxido-reductase inhibitor alone. It reduces hyperuricemia by inhibiting the urate transporter protein URAT1 that is responsible for the majority of the renal reabsorption of uric acid; moreover, Lesinurad also inhibits organic anion transporter OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia. Administration of Lesinurad may be associated with an increased serum creatinine levels therefore renal function should be assessed before initiating therapy and periodically thereafter; more frequent monitoring is required for an estimated creatinine clearance below 60 mL/min and therapy should not be started if creatinine clearance is below 45 mL/min. Lesinurad is not approved for asymptomatic hyperuricemia and it is contraindicated for increased uric acid levels resulting from tumor lysis syndrome [61]. Other uricosuric agents that act on the proximal tubules in the kidneys, where they interfere with the reabsorption of uric acid through blocking URAT1, are Probenecid, Sulfinpyrazone and Benzbromarone. Although these uricosuric agents provide the most time-honoured approach to the control of hyperuricemia, their place in the armamentarium has been eclipsed by that of Xanthine oxidase inhibitors [62].

At last, it is worth noting that some drugs with other primary uses, as Losartan [63], Atorvastatin, Simvastatin [64] and Fenofibrate [65], can have known uricosuric properties; these findings should be considered in hyperuricemic patients with comorbidity as hypertension and dyslipidemia.

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However, regardless of the treatment used, urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 µmol/L) and this value is considered the minimum serum urate target [6,46]. Actually we have found that the relationship between uric acid and cardiovascular events is evident not only in the presence of overt hyperuricemia but also for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range [66-68]. Moreover, a significant independent association between serum urate concentrations and subsequent hazard of incident hypertension was reported even at concentrations below the conventional hyperuricemia threshold of 6.8 mg/dl [20]. At last, the presence of only moderately increased serum uric acid levels (> 5.3 mg/dL in women and > 7.0 mg/dL in men) was also associated with a significantly increased risk of developing type 2 diabetes mellitus [69]. We retain that, regarding the control of serum urate, particularly in patients with other cardiovascular risk factors, the lowest possible value of uric acid is better.

Conclusion

Although some studies have not shown a close correlation between hyperuricemia and cardiovascular risk, most scientific evidence agrees that hyperuricemia plays a key role in determining cardiovascular events and in development of other risk factors often associated also with moderate increases of serum uric acid levels. Early diagnosis, follow-up and prevention programs and effective treatment of hyperuricemia are recommended in particular in patients with other concomitant cardiovascular risk factors. Urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 µmol/L); however, because relationship between hyperuricemia and cardiovascular events is evident also for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range, in high risk patients the lowest possible value of uric acid is better.

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