ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Policlinico S. Orsola-Malpighi

International Symposium on:

FROM GOUT TO CARDIOVASCULAR DISEASE: A CENTRAL ROLE FOR URIC ACID

Bologna (Italy), November 6th - 8th, 2014

Organized by

UNITÀ OPERATIVA MEDICINA INTERNA
AZIENDA OSPEDALIERO – UNIVERSITARIA S. ORSOLA-MALPIGHI
ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA, ITALY

DEPARTMENT OF RHEUMATOLOGY
HÔPITAL LARIBOISIÈRE, PARIS, FRANCE

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ABSTRACT BOOK

Salone Bolognini - Convento S. Domenico (Piazza San Domenico, 13)
Salone Imperiale - Royal Hotel Carlton (Via Montebello, 8)

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From Gout to Cardiovascular Disease: A Central Role for Uric Acid?

Richard J. Johnson
Division of Renal Diseases and Hypertension, University of Colorado, Aurora CO, USA

Uric acid is well recognized as the cause of gout, and an elevated serum uric acid (hyperuricemia, defined as > 7.0 mg/dl in men and 6.5 mg/dl in women) is recognized as a risk factor for this arthritic condition. However, it has been known for decades that subjects with hyperuricemia also often manifest conditions associated with cardiovascular risk, including high blood pressure, obesity, insulin resistance, fatty liver, and chronic kidney disease. For most of the last century the belief was that the presence of hyperuricemia was secondary to these conditions. Indeed, an elevated uric acid could simply reflect the actions of insulin to stimulate urate reabsorption, or impaired excretion from subtle decreases in renal function. Consistent with these findings, a number of studies could not show serum uric acid to be an independent risk factor for cardiovascular events or mortality,[1, 2] leading to the conclusion that uric acid is not a true cardiovascular risk factor, and probably should not even be measured in clinical practice unless there was a concern that the patient may have gout.[3] Similar analyses evaluating the role of uric acid in chronic kidney disease (CKD) came up with similar conclusions.[4] As such, serum uric acid was removed from the routine medical laboratory panel and uric acid was not considered a true cardiovascular risk factor by all major medical societies.

A change in temperament has occurred over the last decade with the realization that the elevation of uric acid often occurs prior to the development of hypertension or metabolic syndrome, making the rise in uric acid difficult to account as a secondary phenomenon. Indeed, multiple epidemiological studies have now provided convincing evidence that an elevated serum uric acid, even in a lean individual with no other cardiovascular risk factors, is an independent predictor for hypertension, obesity, diabetes, fatty liver and chronic kidney disease.[5-9]

Furthermore, the development of a model of mild hyperuricemia in rodents has provided insights into the role of uric acid in several conditions, but especially in hypertension.[10] The model is based on inhibiting the enzyme uricase, which is present in most mammals and degrades uric acid, eventually producing allantoin. Rats in which uricase is inhibited with oxonic acid develop mild hyperuricemia without evidence for intrarenal or extrarenal urate crystal deposition.[10] These animals develop hypertension that can be prevented if the uric acid is lowered with either a xanthine oxidase inhibitor or a uricosuric agent. Studies in the animal model, as well as in cell culture, identified several mechanisms by which hyperuricemia might cause hypertension, including a reduction of endothelial nitric oxide levels, the stimulation of oxidative stress, and activation of the renin angiotensin system.[11-14] Uric acid also stimulates vascular smooth muscle cell proliferation and stimulates the development of microvascular disease in the kidney that histologically is similar to the lesion of arteriolosclerosis.[12, 15] We were also able to show that once hyperuricemia was chronic, that microvascular and inflammatory changes in the kidney led to persistent salt-sensitive hypertension even if the uric acid values were corrected.[16] This suggests that hyperuricemia might play a role in hypertension, especially early hypertension. Consistent with this finding, Dr Daniel Feig has led studies showing a strong relationship of uric acid with hypertension in the adolescent,[17] and has also shown in two small NIH trials that lowering uric acid can lower blood pressure in this population.[18, 19] Hence, an elevated uric acid may be one cause of hypertension, especially in adolescents.

A role for uric acid has also emerged in acute and chronic kidney disease. Several studies have now shown that an elevated serum uric acid is a strong predictor for acute kidney injury, especially following cardiovascular surgery.[20-22] An elevated serum uric acid has also been found to predict the development of chronic kidney disease,[9] and in the subject with diabetes, the development of diabetic nephropathy.[23, 24]

A key study by Kang et al showed that increasing serum uric acid in an animal model of CKD (the remnant kidney model) could lead to more rapid progression,[25] and potential mechanisms include the development of glomerular hypertension[26] and epithelial-mesenchymal transition.[27] Lowering uric acid has also been shown to be protective in animal models of diabetic nephropathy.[28] This has led to a number of small clinical trials that have also shown a benefit of lowering uric acid on slowing renal progression in CKD.[29, 30] Currently there is a large NIH trial ongoing investigating the role of uric acid in diabetic nephropathy.

While the relationship of uric acid with hypertension and CKD are the strongest to date, there is also emerging evidence that uric acid may have a role in features of metabolic syndrome , including fatty liver and insulin resistance. Recently there has been new evidence that activation of AMP deaminase during fructose metabolism may lead to fat accumulation and gluconeogenesis.[31-33] One of the downstream products of AMP deaminase is uric acid, and there is emerging data suggesting uric acid may inhibit AMP activated protein kinase and directly induce oxidative stress in the mitochondria, leading to an inhibition of Beta fatty acid oxidation.[31-33] Lowering uric acid has been found to improve fatty liver and insulin resistance in several animal models, including in the Pound Mouse and in the fructose-fed rat.[34, 35]

The observation that uric acid may have multiple roles in metabolic and cardiovascular disease has led to interest into its potential role in the ongoing obesity and diabetes epidemics. Serum uric acid has been increasing in the population and correlates with the rising epidemics.[36] One potential mechanism could be the intake of sugary foods, as sucrose consists of a disaccharide of fructose and glucose, and fructose generates uric acid during its metabolism.[37] Indeed, there is increasing evidence that fructose-induced hyperuricemia may have a participatory role in the ongoing epidemics. Of additional interest, there is emerging evidence that the uricase mutation that occurred in the Miocene may have acted as a Thrifty Gene,[38] that may have aided ancestral apes to survive famine but at the expense of increased sensitivity to fructose today.[39, 40]

While these studies suggest an important role for fructose and uric acid in driving the epidemics of obesity and metabolic syndrome, there are numerous issues that still need to be addressed. For example, some genome wide association studies have not been able to link polymorphisms driving urate levels with metabolic risk.[41,42] Other studies have shown that uric acid can also have beneficial effects as an antioxidant. Most of all, large clinical studies need to be performed to better assess the role of uric acid in human cardiorenal and metabolic diseases.

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Ancient heart disease and uric acid

Gino Fornaciari
Division of Paleopathology, Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Italy

Reports of cardiovascular diseases in paleopathology are very rare, since the material mainly consists of skeletal remains. We have an Etruscan coarctation of the aorta, cardiac Chagas disease in pre-Columbian mummy severe atherosclerosis of carotid in 15th king, and finally a case of cardiomegaly, possibly secondary to gout, in a Renaissance prince.
Aortic coarctation is a congenital disorder in which a portion of the aorta is narrowed to various extent. A collateral circulation system is enrolled to allow adequate compensation of the blood flow. Collateral vessels may become enlarged, producing a distinctive notching on the pleural surface of the ribs.
Excavation of a 6th to 5th century B.C. Etruscan tomb near Siena (central Italy) revealed three funerary chambers (celle) housing fourteen adult skeletons. The ribs of one of the male skeleton showed typical "nail stroke" indentations. Detailed macroscopic examination enabled us to identify them as notching and led to the diagnosis of post-ductal aortic coarctation. Histological analysis of bone tissue from the notching areas excluded inflammatory and pathological erosive events, supporting the macroscopic diagnosis.
Recently viruses and bacteria were identified, by immunohistochemistry and electron microscopy, in ancient human tissues. These methods have recently been tested on protozoa.
A Peruvian natural mummy**,** a young woman 20±3 years old from Cuzco (Peru), of the Museum of Anthropology and Ethnology of Florence, was autopsied. The funeral equipment was typical of the Andean highlands, pre-imperial Inca culture, 14th-15th century A.D. Macroscopically a megavisceral syndrome in the form of very severe cardiomegaly, megaesophagus, gastric ectasia, and megacolon, with enormous amounts of feces, was found.

Microscopically hematoxylin-eosin and Van Gieson stains showed large fat substitution and fibrosis of the myocardium, fibrosis of esophagus and colon. Therefore the mummy mega-visceral syndrome, together with the myocardial and the gastrointestinal fibrosis strongly suggested a case of Chagas disease, chronic phase, caused by the protozoan parasite *Trypanosoma cruzi*. Giemsa stain evidenced in myocardium and esophagus rare roundish intratissutal nests, about 15-20 μm large, containing several ovular formations (1-2 μm) with small nuclei. The findings correspond morphologically to possible intratissutal nests of amastigotes of *T. cruzi*. For the immunohistochemical study we used immunoperoxidase method, avidine-biotine system. Monoclonal antibodies anti-*T. cruzi* a-Flagellar FCH-F8-1 and FCH-F8-4, produced at the Institute Fatala Chaben of Buenos Aires, were used. The nests of ovular formations and the single formations, if separately examined, showed an intense, selective immunoreactivity at monoclonal antibodies. The ultrastructural study of the hearth tissue showed, on large deposits of collagen fibers, some rare ovular formations with a diameter maximum of 1 μm, characterized by: a double peripheral membrane; microtubules with diameter of about 20 nm; electrondense material, in form of lumps, with a diameter of about 200 nm, identifiable as nucleus; a semilunar elongated body, of about 300x80 nm, identifiable as kinetoplast; a cilinderlike structure, of about 300x30-40 nm, with a more electrondense thickening at one end, identifiable as axoneme with its basal body. The evidenced structures were peculiar to anastigotes of the *Trypanosomatídae* famíly. Therefore the macroscopic, histological, immunohistochemical and ultrastructural findings clearly show that we are in presence of an old case of chronic Chagas disease. We have here the first direct demonstration of a case of severe cardiac Chagas disease and its etiological agent in the south-American continent during the Inca civilization.

Atherosclerosis is often considered a modern disease, associated with contemporary lifestyle; however, vascular calcifications and plaques have been identified in ancient human remains, mainly in Egyptian mummies of people belonging to the elite classes.

Various factors have been considered in the pathogenesis of atherosclerosis, including genetic predisposition and environmental factors such as obesity, exposure to smoke and composition of diet that is rich in cholesterol and saturated fats.

The mummy of Ferrante I of Aragon (1424-1494), King of Naples and one of the most important personalities of the Italian Renaissance, was exhumed from its sarcophagus in the monumental sacristy of the Basilica of San Domenico Maggiore in Naples (southern Italy). The dry microclimatic conditions of the church, where several mummies of Renaissance Aragonese princes and noblemen are preserved, as well as the substances used for embalming, favored an excellent state of preservation of soft tissues and internal organs. A comprehensive autopsy was performed on the king's mummy, and different tissues were sampled. Macroscopically, the right common carotid artery appeared distorted and calcified, with an irregular and bumpy wall due to a severe atherosclerosis; however, the lumen was open. Samples of the artery, rehydrated in Sandison's solution, were stained with hematoxylin and eosin and with Weigert's method for elastic fibers. Some frozen sections, 7-μm thick, were stained with Oil Red solution, to identify neutral triglycerides and lipid deposits. Atherosclerosis was confirmed by the histological findings in terms of an intense red core of oil red-positive amorphous material, surrounded by a foamy substance, i.e. the atheroma, lying on a well-preserved elastic wall. Some granular fragments of calcium were present at the periphery of the vessel, with several empty spaces, in the form of needle-like lacunae, caused by crystals of cholesterol dissolved by routine histological methods. This complicated plaque ulcerated, with abundant foamy material circumferentially protruding in the lumen, which could have occluded the artery easily. The smooth muscle of the wall appeared to be largely replaced by fibrous tissue in the form of longitudinal stripes between the *laminae*, spaced out by minute empty areas. This is a clear picture of sclerosis and elastosis, with disintegration of the elastic fibers and neoformation of parietal collagen tissue.

An artistic representation of the king, a statue of Ferrante in advanced age sculpted by Guido Mazzoni in 1492, 2 years before his death, shows the marked profile of a tortuous and salient temporal artery, which suggests a severe and diffuse arteriopathy. Nevertheless, contemporary chronicles describe that he had a very active lifestyle with horse riding and hunting, which suggests that the cerebral circle functioned competently.

Finally, I presents a case of renal calculosis affecting a 15th century Italian nobleman. The natural mummy of Pandolfo III Malatesta (1370-1427), prince of Fano and leading figure of the Italian Renaissance, was exhumed from his monumental tomb in Fano in 1995. Pandolfo was Captain General of the troops of the Venice Republic in the war against the Visconti of Milan and the Hungarians.

Previous paleopathological studies revealed the typical ergonomic picture of a horseman and a soldier. Obesity, attested by large cutaneous folds, and prostatic nodular hyperplasia were diagnosed. Autopsy of his well preserved natural mummy revealed severe cardiomegaly, with massive enlargement of entire hearth, left and right. A roundish calculus of 1.2 cm in diameter was observed in the left kidney. The stone surface was examined by binocular stereoscopic microscopy and scanning electron microscopy and X-ray diffraction analysis. At stereoscopic microscopy, the mulberry-like stone surface, honey brown in color, consisted of aggregated large crystals; at scanning electron microscopy, structures referable for their dimensions to fungi and large *cocci* are visible. X-ray diffraction analysis revealed that the calculus was formed by ammonium acid urate (95%) and calcium oxalate dihydrate (weddellite) (5%), as shown by the diffractgram.

Stones with pure ammonium acid urate are uncommon; ammonium acid urate is generally the predominant crystal associated with other components, such as calcium oxalate. Risk factors for ammonium urate urolithiasis, whose occurrence in modern clinical practice of industrialized countries is low, include repeated urinary infections, obesity, and a diet poor in phosphate and fluid intake.

Since serum uric acid represents an important, independent risk factor for cardiovascular and renal disease in patients with hypertension, obesity, heart failure, or diabetes, it is highly probable that Pandolfo, producing this acid urate stone, developed severe hyperuricemia or gout, with possible important pathogenic role in his cardiovascular disease.

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Biochemistry of Uric Acid in Clinical Perspective

F. Perez-Ruiz
Rheumatology Division, Cruces University Hospital, Vizcaya, Spain

The raise in serum urate levels in upper apes due to the loss of expression of the uricase gene has been considered an evolutive adaptation either as free radical excavenger or to increase arterial pressure (1). Interestingly, also a mutation in the URAT1 sequence appears to have happened close in time during evolution to enhance renal tubular reabsorption of urate (2). Thus, the raise in urate levels is in apes is unlikely to be casual.

Although hyperuricemia may be the result of damage of diseases involving organs that regulate serum urate levels, such as in chronic kidney disease, inherited genetic factors, such as polymorphisms or renal and intestinal transporters of urate have been recently demonstrated to be non-modifiable risk factors for hyperuricemia (3). In addition, environmental factors may interact with genetic predisposition to further increase (4) of serum urate levels through a decrease in the renal clearance of urate (5).

Sustained hyperuricemia is a requisite for the nucleation of monosodium urate crystals (MSUCs); the orderly array of MSUCs may indicate process of epitaxial, template mediated formation based on templates of proteins in the cartilage and soft tissues, although to date no polymorphism of such proteins has been yet demonstrated to explain subject susceptibility to MSUCs deposition. Despite acute episodes of inflammation due to the shedding of MSUCs to synovial-lined structures are the clinical paradigm of gout, subclinical inflammation may be at work in the early phases of MSUCs deposition in tissues (6). Once again, genetic predisposition to MSUCs-induced inflammation has been recently shown, as polymorphisms in toll-like receptors is associated to the development of clinical manifestations of gout (7) in caucasian subjects.

On the other hand, variants is xanthine-oxidase (XO) have been observed influence XO activity (8) and also been associated to the risk of hypertension (9).

These findings have obvious implications for the consideration of XO overactivity as a vascular risk factor, but also has therapeutic implications as whether to target urate, XO, inflammation or all in patients with gout and vascular risk factors (10).

In summary, hyperuricemia and gout seem to be a complex pathophysiologic network in which genetic predisposition for urate handling and MSUCs-induced inflammation, environmental factors, medications, and renal damage may be overlapped, the extent of any of this factors being variable depending on individual and racial bases. Targeting just serum urate may not just be enough for patients with gout and increased vascular risk.

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Uric acid: from molecular mechanisms to human vascular damage

Claudio Ferri
University of L'Aquila, Dept. MeSVA, Division of Internal Medicine and Nephrology, San Salvatore Hospital, L'Aquila, Italy

Several experimental and clinical studies reported that hyperuricemia may trigger hypertension, metabolic syndrome, vascular damage and renal disease. Furthermore, a substantial proportion of epidemiological studies are compatible with the hypothesis that hyperuricemia may be an indipendent risk factor for cardiovascular disease as well as for an increased cardiovascular mortality. Xanthine oxidase is a critical source of reactive oxygen species contributing to vascular inflammation and endothelial dysfunction. Although a causal relationship between these conditions has not been clearly clarified, the capacity of uric acid to negatively affect vascular function by pro-oxidant effects and by decreasing nitric oxide bioavailability and consequently induce endothelial dysfunction may explain the association among hyperuricemia, hypertension, the metabolic syndrome, and cardiovascular disease, also by a common mechanicistic point of view. Concordant to this, we have recently investigated the relationship among serum uric acid levels and metabolic syndrome. Anthropometric parameters, serum uric acid and metabolic parameters were evaluated in 139 subjects, showing that serum uric acid levels were significantly higher in subjects with than without metabolic syndrome ($p < 0.0001$). Of note, the same levels raised gradually with the increasing number of metabolic syndrome components (p for trend < 0.0001). Serum uric acid levels also significantly correlated with various anthropometric and serum metabolic parameters. Thus, we were able to conclude that serum uric acid levels were higher in individuals with than without metabolic syndrome and raised gradually as the number of metabolic syndrome components increased. The relationship between serum uric acid levels and various metabolic parameters further support the role of uric acid as a component/determinant of the metabolic syndrome.

The Role of the Inflammasome Between Uric Acid and Gout

Michael A. Becker
Department of Medicine, University of Chicago, Chicago, USA

Acute inflammation - An intense inflammatory response initiated in the synovium by monosodium urate (MSU) crystal deposition, or more often by release of MSU crystals from preformed deposits, is characteristic of acute gouty arthritis and underlies the symptoms and signs of the gout flare. Synovial lining cell hyperplasia and infiltration by neutrophils, monocytes/macrophages, and lymphocytes are major histologic features of this process.[1] The predominance of neutrophils and neutrophil phagocytosis of MSU crystals in the synovial fluid aspirated from an acute gouty joint initially focused attention on inflammatory processes mediated by neutrophils in the pathogenesis of acute gout. However, identification of multiple additional events preceding or accompanying neutrophil activation has contributed to further understanding of the multiple processes involved in initiation and amplification of MSU crystal-induced inflammation.[2] For example, synovial mononuclear cells, dendritic cells, and endothelial cells all ingest MSU crystals and release proinflammatory cytokine and chemokine mediators, and phagocytosis of MSU crystals by synovial lining cells precedes the influx of neutrophils into the joint in vivo.[2,3]

Studies of MSU crystal-induced inflammation in the past decade have revealed and confirmed the importance of processes activating the innate immune system that are shared with rare inherited disorders, such as the cryopyrin-associated periodic syndromes (CAPS)[4] and have shown that MSU crystals derived from urate released from cells undergoing "sterile" cell death can also serve as a danger signal, activating both innate and adaptive immune responses.[3,5] Understanding the primacy and interactions of pro- (and anti-) inflammatory processes induced by MSU crystals and how environmental factors, including comorbidities, affect (and are affected by) these processes remains a work in progress.

Still, considerable insight has been gained in identifying mediators of the sequential events in acute gouty inflammation: initiation, amplification, and resolution. This presentation will address only the initiation and amplification phases of acute gout. Resolution of acute gout and chronic gouty inflammation, as encountered in tophaceous gout and gouty arthropathy, are discussed elsewhere.[6,7]

Initiation of acute MSU crystal-induced inflammation - The initiation of the acute inflammatory response to MSU crystals is affected by properties of the crystals themselves and proteins coating the crystals, cell-mediated mechanisms including signaling via membrane receptors, assembly and activation of the NLRP3 inflammasome, and the release of multiple cytokines.

Certain properties of MSU crystals, including size, electrostatic charge, state of aggregation, and the presence and nature of proteins coating the crystals may impart or restrain the proinflammatory potential of MSU crystals deposited in the joint. For example, MSU crystals derived from tophi produce more inflammation than synthetic crystals, a difference eliminated by protease treatment of tophi.[8] Binding of immunoglobulin G (IgG) to MSU crystals results in an increased release of superoxide and lysosomal enzymes from human neutrophils in vitro compared with protein-free, crystal-induced release of these substances.[9] These findings imply an amplification rather than initiation phase effect for crystal-IgG binding. However, reduction in the inflammatoty potential of MSU crystals bound by lipoproteins (particularly apolipoprotein B) prior to injection in animal models[10] suggests that lipoprotein binding to crystals contributes to the resolution of acute gout and, perhaps, also to the absence of MSU crystal-induced attacks in the joints of some gout patients in whom MSU crystals persist over the course of many months or years.

MSU crystal cell-mediated mechanisms supporting or essential for the initiation phase of MSU crystal-induced acute inflammation include: membrane signaling through Toll-like receptors (TLR)-2 and TLR-4;[11] and expression of MyD88, an adaptor protein (CD14) shared by TLR-2

and TLR-4, and TREM 1 (triggering receptor expressed on myeloid cells 1).[12-14] Conflicting data have been presented regarding the necessity of one or more of these mechanisms, but a central role for resident macrophages in the initiation of acute MSU crystal inflammation is widely acknowledged.

Activated monocytes and synoviocytes release interleukin-1 (IL-1), Il-6, IL-8, and tumor necrosis factor (TNF) in response to MSU crystals in vitro,[2] and increased levels these proinflammatory agents are found in gouty tissues in vivo. A major advance has been identification of MSU crystal-induced assembly and activation of the NLRP3 (NOD-like receptor NLRP3) inflammasome, with consequent caspase-1-catalyzed pro-IL-1 processing and release of IL-1β from macrophages and activated monocytes.[15] This work, has clarified the sequence of molecular events related to initiation and amplification of MSU crystal-induced inflammation.[15,16] Upon exposure to MSU crystals, inactive NLRP3 is released from a complex with heat-shock protein 90 (HSP90) and the suppressor of G2 allele of SKP1 (SGT1), oligomerizes to a conformational state that permits binding to the ASC (apoptosis-associated speck-like protein containing a CARD domain) adaptor protein and latent caspase-1. In the resulting active NALP3 inflammasome complex, caspase-1 is activated to catalyze conversion of pro-IL-1 to IL-1 with subsequent secretion of the active cytokine, IL-1β. Recruitment and activation of neutrophils, monocytes, dendritic cells, and other inflammatory cells appear to be dependent upon locally produced cytokines, and IL-1β is a cytokine critical for initiation of gouty inflammation.[3] Rodents deficient in IL-1 receptors do not mount as vigorous an inflammatory response as wild-type animals do to injected MSU crystals, and clinical trials showing the efficacy of IL-1 antagonists in treatment and/or prophylaxis of acute gout flares support an important role for IL-1 mediation in acute gout.[17]

A study utilizing human peripheral blood mononuclear cells (PBMCs) and murine macrophages found that free fatty acid engagement of the toll-like receptor, TLR-2, on human PBMCs resulted in a synergistic increase in MSU crystal-induced IL-1β release that was

dependent upon activation of components of the NLRP3 inflammasome.[18] Interestingly, synergy between MSU crystals and TLR-2 ligands in IL-1 and IL-6 release is greater in PBMCs derived from gouty than from non-gouty persons,[19] suggesting a possible basis for the clinical observation that constitutional events such as dietary indiscretions provoke acute gout attacks.[20]

Amplification of acute MSU crystal-induced inflammation - Neutrophils provide a central cellular mechanism for amplification of acute gouty inflammation, a role accurately reflected both by the synovial histology and the leukocyte profile of synovial fluid aspirated at clinical presentation of the human gout flare. Neutrophil recruitment to the joint requires cellular and fluid phase proinflammatory processes, such as mast cell degranulation, activation of the complement cascade, and expression of endothelium-derived selectins, which play their major roles in the neutrophil-centered amplification of inflammation.

Activation of the endothelium of blood vessels adjacent to the joint is mediated by MSU crystal-induced participation of activated resident macrophages, chondrocytes, mast cells, and dendritic cells, and by activation of both classical and alternative complement pathways.[2] Endothelial cell activation results in vascular dilatation and increased vascular permeability as well as endothelial cell expression of adhesion molecules, including E-selectin, intercellular adhesion molecule-1 (ICAM), and vascular cell adhesion molecule-1 (VCAM).[2] As a consequence, neutrophils in the circulation undergo events leading to adhesion to the endothelium and traversal of the vessel wall. Extravasated cells then follow the concentration gradients of chemotactic molecules to the site of inflammation.[2] The major chemotactic molecule involved in crystal-induced inflammation is IL-8, with leukotriene B4, IL-1, and complement fragment C5a also contributing.[21]

Neutrophils are involved in a positive feedback loop of inflammation. Once in the inflamed joint, neutrophils are subject to either crystal phagocytosis-induced degranulation or direct crystal lysis of lysosomal membranes,2 with the release of further inflammatory

mediators (prostaglandin E2, nitric oxide, leukotriene B4 [LTB-4], reactive oxygen species, S100A8, S100A9, IL-1 , and IL-8), as well as mediators of pain and tissue damage. The fact that most neutrophils in synovial fluid in acute gout do not contain detectable crystals suggests that they may contribute to inflammation in ways not requiring crystal phagocytosis. MSU crystals also recruit and activate monocytes/macrophages to express proinflammatory molecules, including IL-1, IL-6, IL-8, TNF-alpha, cyclooxygenase-2 and LTB-4.[2]

MSU crystal activation of fluid phase inflammatory/nociception mediator systems includes the classical and alternative complement pathways; formation of the complement membrane attack complex, which activates endothelial cells to produce potent neutrophil chemotaxin, IL-8; the kallikrein-kininogen pathway (the product, bradykinin, contributing to vascular endothelial cell activation); prostaglandins; and substance P and LTB4, which are nociceptor sensitizers that result in the heighted pain associated with acute gout.[2,21-23] The cellular biology and intracellular signaling mechanisms involved in neutrophil chemotaxis and activation in response to crystals are complex, involving transcriptionally and post-transcriptionally determined changes in the actions of kinases, phospholipases, chemoattractants, adhesion molecules, and other factors.

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Genetics of Gout

R.J. Torres
Metabolic Vascular Risk Unit, Purine Laboratory, La Paz Hospital, IdiPaz, Madrid, Spain

Gout is a purine metabolic disease characterised by acute, recurrent attacks of arthritis caused by monosodium urate crystals deposits. The single most important risk factor for gout is an increased level of serum urate (sUA). Super-saturation of uric acid in the extracellular fluid results in the precipitation of monosodium urate crystals in joints, kidney and soft tissues (1). Hyperuricemia may be the result either endogenous overproduction (synthesis and cell turnover) or urinary underexcretion of urate (2).

Monogenic causes of hyperuricemia account for a small percentage of total gout. Two main congenital purine metabolic enzyme defects have been described that markedly increase uric acid synthesis. One is located at *de novo* purine synthesis (phosphoribosyl pyrophosaphate synthetase overactivity) (3), and the second at the salvage pathway (hypoxanthine phosphoribosyltransferase deficiency) (4). Some enzyme defects of carbohydrate metabolism (glycogen storage diseases I, III, V and VII types and hereditary fructose intolerance) have also been associated to hyperuricemia and gout. Finally, a congenital decreased of uric acid excretion is found in Familial juvenile hyperuricemia nephropathy (FJHN). This is an autosomal dominant renal disease characterized by juvenile onset of hyperuricemia, gouty arthritis, and progressive renal failure at an early age. More than 58 different mutations in the *UMOD* gene have been reported (5). However, FJHN is characterized for genetic heterogeneity. Thus, mutations in other regions or genes, as REN gene and in HNF1B (hepatocyte nuclear factor 1 beta) gene, have been less frequently found as a cause of the disease.

Genetic polymorphisms, hyperuricemia and gout. Renal urate underexcretion is the main mechanism of hyperuricemia in about 90% of the patients with primary gout.

The renal excretion of urate depends on renal tubular reabsorption and secretion, mechanisms involve ion transporting proteins at the proximal renal tubule. To date, no mutations in these urate-transporter-protein coding genes have been found as a cause of congenital gout (6). However, near 25-40% of gouty patients have a positive familial history of gout and, in family-based studies, sUA has been found to be significantly heritable. In the last years, several reports, including a number of genome-wide association studies, have identified a substantial association between single nucleotide polymorphisms (SNPs) in as many as 28 genetic loci, including 6 urate-transporter-protein coding genes, and both sUA and gout. In a recent study (7), we have determined three reabsorption (*URAT1, GLUT9, and OAT4*) and two secretion transporter genes (*NPT1 and ABCG2*) SNPs in 104 patients with primary gout, classified as normoexcretors and underexcretors according to the relation between sUA and 24h urinary uric acid excretion (2). Compared to control subjects, patients with gout showed different allele distributions of the five SNPs analyzed. However, gouty underexcretors showed an association with the transporter gene SNPs related mainly with tubular reabsorption, whereas uric acid normoexcretion was only associated with tubular secretion SNPs (7). A strong association was found in all study subjects between the presence of allele T of *rs11231825* (*URAT1*), allele G of *rs16890979* (*GLUT9*), and allele A of *rs2231142* (*ABCG2*) and higher sUA. An individual genetic risk score was generated by counting the number of alleles of those genes associated with sUA in our population (range 0 to 6 points according to the number of risk alleles). The proportion of subjects across the genetic risk score showed a markedly different distribution, with control subjects and gout patients skewed to the lower and upper risk scores, respectively. Mean sUA in the entire population increased linearly with the number of risk alleles (χ^2 =20.035, P=0.0027). In addition, the prevalence of gout also increased linearly with the number of risk alleles. The odds ratio (OR) for the diagnosis of primary gout increased significantly for those patients with $\geq$3 risk alleles.

For subjects with no risk alleles, the crude prevalence of gout was 0.257 and increased to 52.478 for those with six risk alleles (208-fold increased). The finding of a significant correlation between the genetic risk score and both sUA and the prevalence of gout can best be interpreted as an indication that certain SNPs markedly determine the kidneys' handling of urate (7). This suggests that knowledge of patients' genotypes could help identify individuals at risk of gout, such as those with metabolic syndrome or cardiovascular diseases, long before the onset of clinical features, and may help guide clinical decisions, particularly when considering drugs known to increase sUA.

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Genes Uric Acid and CV Diseases

Jesse Dawson
Institute of Cardiovascular and Medical Sciences, University of Glasgow Western Infirmary, Glasgow, United Kingdom

Serum uric acid level is associated with incident hypertension and increased cardiovascular risk in a variety of patient groups. However, influences on serum uric acid level are multifactorial and include environmental factors drugs such as thiazide diuretics, diet, and a number of putative genes.
A small number of monogenic disorders are associated with hyperuricaemia and gout. These include activating mutations in the phosphoribosyl pyrophosphatatse synthetase gene, inactivating mutations in the hypoxanthine guanine phosphoribosyl transferase gene (Lesch-Nyhan syndrome) and mutations in the uromodulin gene. Numerous candidate genes have been reported to be involved in regulation of serum uric acid level (table 1) via genome wide association studies (GWAS). In the study to date, 26 were identified and replicated via GAWS and a further 2 via pathway analysis (1). An association with four other candidate genes has been reported in other studies (2). The proportion of variance in serum uric acid explained by these genes is approximately 5 to 7%. Candidate genes encode either urate transporters, proteins involved in glucose metabolism and insulin response, proteins which interact with urate transporters, transcription factors or growth factors or gene products with unknown or poorly described function with an unclear relationship with uric acid regulation.

Gene	Gene Product	Putative Role in Regulation of Urate Level
A1CF *	APOBEC1 complementation factor	Unknown
ABCG2 *	ATP Binding Cassette B member 2	Urate transporter
ARNT *	Aryl hydrocarbon receptor nuclear translocator	Unknown, interacts with transcription factors
ATXN2 *	Ataxin 2 protein	Unknown
BAZ1B *	Bromodomain protein	Unknown
BCAS3 *	Unknown	Unknown
GCKR *	Glucokinase regulatory (inhibitory) protein	Unknown, role in glucose metabolism
HLF *	Proline and acidic rich transcriptor factor family	Unknown, transcription factor
HNF4G *	Hepatocyte nuclear factor 4	Growth factor
IGF1R *	Insulin like growth factor 1 receptor	Unknown, role in glucose metabolism
INHBB *	Activin B	Unknown
INHBE *	Beta chain of inhibin	Unclear, TGF-B superfamily
LRRC16A #	Leucine rich repeat containing 16A	Unknown
MAF *	MAF protein	Unknown, transcription factor
NFAT5 *	Nuclear factor of activated T cells 5	Unknown, role in glucose metabolism

NRXN2 #	Neurexin family protein	Unknown, cellular adhesion molecule
ORC4L *	Origin recognition complex subunit 4	Unknown
OVOL1 *	OVOL 1 protein	Unknown, putative trabscription factor
PDZK1 *	PDZ domain containing 1 protein (scaffolding protein)	May interact with urate transporters
PKD2 #	Polycystin 2	Unknown
PRKAG2 *	5'AMP activated protein kinase subunit gamma 2	Unknown, role in glucose metabolism
QRICH2 *	Glutamine rich protein 2	Unknown
RREB1 *	Ras responsive element binding protein	Unknown, transcription factor
SFMBT1 *	SCM like protein with four MBT domains	Unknown
SLC16A9 *	Monocarboxylic acid transporter 9	Unknown, role in glucose metabolism
SLC17A1 #	NPT1 (renal sodium phosphate transporter protein 1)	Urate transporter
SLC17A3 *	NPT4 (renal sodium phosphate transporter protein 1)	Urate transporter
SLC22A11 *	Solute carrier family 11 r (related to URAT1)	Urate transporter
SLC22A12 *	URAT1	Urate transporter
SLC22A7 *	Organic anion transporter 2 (OAT2)	
SLC2A9 *	GLUT 9	Urate transporter

STC1 *	Stanniocalcin 1	Unknown
TMEM171*	Transmembrane protein	Unknown, putative growth factor
TRIM46 *	TRIM46 Protein	Unknown, Incorporates a motif associated with microtubule binding.
UBE2Q2 *	Ubiquitin conjugating enzyme member 2	Unknown
VEGFA *	VEGFA	Unknown, growth factor
* identified and replicated in study by Kottgen et al (ARNT and SLC22A7 were identified and replicated using pathway analysis). # association reported in study by Kolz et al (and others) but not by Kottgen et al.		

The ranging products form these putative genes provide important pathophysiological insights into uric acid regulation and its potential role in cardiovascular diseases and this will be discussed during this presentation.

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The interaction between gout and other rheumatic diseases: current trends

P. Richette
Department of Rheumatology, Hôpital Lariboisière, Paris, France

Gout is a common arthritic condition caused by deposition of monosodium urate crystals in joints after longstanding hyperuricaemia. Urate concentrations vary greatly among patients, and the level in a given patient is thought to result from a combination of genetic predisposition, environmental factors and presence or not of comorbidities (1).
Patients with gout often have comorbid conditions such as obesity, cardiovascular disease, renal failure and components of the metabolic syndrome (2). Some of these comorbidities are also known risk factors for other rheumatological conditions, in particular osteoarthritis (OA), which prevalence is very high. Thus, OA is often encountered in patients with gout.
However, gout shows a striking predilection to affect certain joints, most strikingly the first MTP joint. Although it is not known why gout demonstrates such a characteristic pattern, the first MTP joint is also a target joint for OA and it has been postulated that MSU crystals may deposit more readily in osteoarthritic cartilage. Radiographic and clinical studies support the tendency of gout to occur at joints already affected by OA (3,4).
Several studies have shown a correlation between psoriasis, psoriatic arthritis (PsA) and elevated serum uric acid levels. It was shown recently that PsA was associated with an increased risk of gout, in particular in men (5).
Other rheumatic diseases which have been described in patients with gout are rheumatoid arthritis, septic arthritis and chondrocalcinosis (6,7,8). Whether these associations are fortuitous or not, due to the high prevalence of gout, is unknown.

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Urate Crystal Deposition and Gout: Epidemiology and Clinical Evidence

Leonardo Punzi
Rheumatology Unit, Department of Medicine DIMED, University of Padova, Italy

Gout is the most frequent inflammatory arthropathy in the population. Furthermore, it has been suggested that there is an increasing trend in the prevalence of hyperuricemia and gout in Western countries during the last few decades (1-3). Population-based studies estimated prevalence of 21% for hyperuricemia and 4% for gout during the years 2007–2008 in the US and 1.4% for gout in the UK and Germany during the years 2000–2005 (4,5). In Italy, a recent nationwide population-based study observed during the period 2005-2009 an increase of the prevalence of hyperuricemia from 8.5% in 2005 to 11.9% in 2009, and of gout from 0.7% in 2005 to 0.9% in 2009 (6). According with these data, it seems that the prevalence of hyperuricemia in Italian people was lower than that reported from other countries (6,7). As regard the social-economic consequences, in the recently published Global Burden of Disease (GBD) 2010, gout disability-adjusted life years DALYs increased from 76 000 (95% UI 48 to 112) in 1990 to 114 000 (95% UI 72 to 167) in 2010 (8). Out of all 291 conditions studied in the GBD 2010 Study, gout ranked 138th in terms of disability as measured by YLDs, and 173rd in terms of overall burden (DALYs).

Taken together, the above epidemiological data suggest a progressive increase worlwide of serum levels of uric acid. This rise in the prevalence of hyperuricemia and gout may be related to the epidemic diffusion of overweight and obesity as well as the shifts in diet with increased consumption of foods rich in purines, alcoholic consumption, and soft drinks sweetened with fructose (9-11). According to this hypothesis, the mean serum uric acid levels are risen in United States from 3.4 mg/dL in 1920s to 6.25 mg/dL in 1970s (7).

Classically, the most common clinical expression of gout is an acute attack or flare involving the the first metatarsophalangeal joint (podagra) with a typically abrupt onset evolving in 6-12 hours, and with the affected joint painful, tender, erythematous, warm, and swollen (12). In some cases, the first presentation of acute gout may occur in other joints, in particular knees, ankles, wrists, and elbows. Gout flares can be polyarticular in women and elderly, with sometimes a more chronic and indolent evolution and an increased incidence of tophi (13). As a result, gout in the elderly can be mistaken for changes that are usually attributed to osteoarthritis or rheumatoid arthritis, thus requiring a particular attention by the clinicians in making diagnosis.

Most often monosodium urate (MSU) crystals are released from preformed deposits in the joints, the so called "microtophi", which can be asymptomatic or silent for many years. As demonstrated by recent studies by utilising sensitive imaging techniques, such as MRI and/or ultrasound, a large percentage of patients with gout and normal plain radiographs may reveal also a destructive arthropathy (14,15). Usually, when left untreated acute attacks of gout can lead to chronic gout, which is characterized by chronic destructive polyarticular involvement with low-grade joint inflammation, joint deformity, and tophi (12,16). However, the classic idea that tophaceous gout may develop within 5-10 years of onset of gout need to be redefined. Accordingly, a new clinical staging system for gout was recently proposed by Dalbeth and Stamp (17); A: hyperuricemia but without evidence of MSU crystal deposition of symptoms of gout; B: MSU crystal deposition by microscopy or advanced imaging; C: MSU crystal deposition with prior or current symptoms of acute gout flares; D: advanced gout requiring specialist interventions. However, the definition of hyperuricemia should be carefully updated according with the its role as risk factor not only for gout, but also for renal and cardiovascular diseases.

In this context, a growing consensus seems obtained by the proposal that hyperuricemia, the level at which uricemia becomes abnormal, should be defined for serum uric acid levels greater than 6mg/dl, as the life-long

risk of gout seems to start at this level (7,18). Furthermore, this definition is in keeping with the minimum uricemia target of urate-lowering drugs.

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Diagnosis of Gout in Patients with Asymptomatic Hyperuricemia

García-Puig J.
Metabolic-Vascular risk unit, Division of Internal Medicine, La Paz University Hospital, IdiPAZ, Madrid, Spain

Asymptomatic hyperuricemia is a very frequent condition. Among 503 subjects, aged 35 to 70 years, randomly selected from the Caucasian Madrid general population (men, 45%) we found a serum urate concentration ≥7.0 mg/dL in 13.4% (95% CI, 10.4-15.9). Among these patients the prevalence of metabolic syndrome (ATPIII criteria) was 53,1% (95% CI, 40,9-65,3) and among subjects without this condition 24.4% (95% CI, 20,3-28,4) ($p<0.001$). Mean serum urate gradually increased with increasing number of metabolic syndrome components and correlated with waist circumference ($r=0.456$; $p<0.001$). The prevalence of metabolic syndrome among patients with asymptomatic hyperuricemia is much higher in other countries (US population, >40%) (2). According to expert panels of rheumatologists, asymptomatic hyperuricemia should not be pharmacologically treated to prevent gouty arthritis, renal disease or CV events (3). Since asymptomatic hyperuricemia is commonly associated to conditions that increase CV risk and in itself causes inflammation due to crystal deposition, the question arises as to whether asymptomatic hyperuricemia is a "benign conditon". Four studies have documented ultrasonographic signs of urate deposits in subjects with long-standing (≥2 years) asymptomatic hyperuricemic (4-7). Our group has documented signs of urate deposits (tophi, double contour sign, and hyperechoic spots in synovial fluid) located in tendons, synovium and other soft tissues in two series of asymptomatic hyperuricemic patients (in 12 out of 35 patients [34%[[4] and in 11 out of 26 patients [42%] [7]). Eight patients of the former series (24%) showed inflammation (increased vascularity with doppler ultrasound) (4). In 9 out of 11 patients (82%) of the later series ultrasound signs of urate deposits were confirmed (compensated polarising microscopy) (7).

From both studies we may conclude: (a) long-standing (≥2 years) asymptomatic hyperuricemia may lead to soft tissue urate crystal deposition in about one third of the patients; (b) inflammation can be detected in most of patients with urate deposits, and (c) it is debatable whether these patients may benefit from urate lowering therapy to clear off urate deposits and inflammation.

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The management of gout arthritis in the era of guidelines

Thomas Bardin
Université Paris 7 and Lariboisière Hospital, Paris, France

Gout is the most common form of arthritis, especialy in men (1). It is due to the deposition of phlogenistic monosodium urate (MSU) crystals in the joints following chronic serum uric acid increase above the saturation point (2). Lowering urate levels under 6 mg /dL (360 micromoles /L) allows dissolution of crystal deposits and disappearance of gout features. Despite being highly curable, gout is an increasing health problem and is seldom properly treated (3). This has led several scientific societies to issue guidelines with the aim of improving gout management (4-6).

- Education plays a key role in gout management. Most of treatment failures are due to poor urate lowering drug adherence. A recent pilot study has shown that following proper patient education, patients met long term urate target lowering and clinical control of the disease, as adherence became optimal (7). The recently revised EULAR recommendations state that "every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities, and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA below a target level"(8). Advises on lifestyle are also important, especially the avoidance of beer, non diet sodas and spirits.
- Urate lowering under the saturation point for MSU is a key point of gout managements as it allows dissolution of the crystal deposits and disappearance of disease features. Urate should be lowered under the target of 6 mg/d (4), and even lower, to 5 mg/dL, in severe gout, in order to increase the speed of crystal dissolution (5,8). Indications for urate lowering drugs are on the increase.

  The last EULAR task force recommended to consider ULDs as soon as the diagnosis is made (8), as early gout appears to be

easier to treat and the poor cardiovascular prognosis of gouty patients could be improved by ULDs. Prophylaxis of ULD-induced attacks, by small dose colchicine, is recommended by all professional societies, for 6 months, according to the last version of the EULAR recommendations. The EULAR also recommends progressive titration of ULDs, in order to decrease triggered flares.

- The two xantine oxydase inhibitors, allopurinol and febuxostat, are recommended as first line ULDs by the ACR (6), whereas the EULAR recommended allopurinol only as first line ULD (8). Allopurinol titration is viewed as very important by both societies in an attempt to decrease the incidence of severe adverse cutaneous reactions (SCARs)(6,8). According to the ACR, allopurinol dose should be increased even in renal failure patients, above the classical maximal dose as a function of creatinine clearance (6), whereas the EULAR recommends to respect this limitation and to shift to febuxostat or benzbromarone when the uricemia target cannot be met (8). Both societies acknowledged the possibility to associate uricosurics to XO inhibitors and the indication of pegloticase in severe refractory gout.
- Drugs to be used for the management of acute flares include colchicine, NSAIDs and steroids, alone or in combination. Colchicine is efficient at low doses at the onset of acute flares and should be used only in the first 48 (6) or 24 hours (8) of flare onset. IL-1 blocking is recommended by the EULAR for the treatment of acute flares in patients with definite severe gout resistant or contraindicated to colchicine, NSAIDs and steroids.

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Uric Acid in the Development of Hypertension: Experimental Data

Marilda Mazzali
Division of Nephrology, Department of Medicine, State University of Campinas, Campinas (Brazil)

Hyperuricemia is associated with hypertension, kidney disease, vascular and cardiovascular events[1]. In experimental animals inhibition of hepatic uricase induces hyperuricemia, hypertension and mild renal disease[2]. The microvascular changes observed in the experimental model of hyperuricemia resembles the histological changes of human hypertension, as well as vascular remodeling and interstitial inflammation observed in the spontaneous hypertensive rat (SHR).

The initial mechanism by which uric acid causes hypertension appears to be via endothelial dysfunction, through activation of the renin angiotensin system[2], inhibition of endothelial nitric oxide production[2,3], and the induction of oxidative stress[3], that results in vasoconstriction of preglomerular arterioles and increased blood pressure. This effect can be reversed by normalization of uric acid levels. Uric acid also mediates vascular smooth muscle cell function, leading to proliferation and vascular remodeling, aggravating hypertension that becomes refractory to correction of hyperuricemia. Persistent hyperuricemia results in afferent arteriolopathy that is associated with renal vasoconstriction and salt sensitive hypertension[4], as well as with glomerular hypertrophy and glomerulosclerosis [5]. The relationship between hyperuricemia, hypertension (vascular remodeling) and tubulointerstitial damage creates a vicious circle that perpetuates and aggravates hypertension and progression of renal damage. Experimental models showed that hyperuricemia aggravates the progression of renal disease in cyclosporine nephropathy and remnant kidney disease models[6,7], and normalization of uric acid levels were associated with a protective effect [8].

Clinical data suggests that treatment of hyperuricemia improves endothelial dysfunction and glomerular filtration rate in subjects with asymptomatic hyperuricemia [9]; prevents hypertension in children[10] and promotes cardiovascular protection[11].

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Uric acid and hypertensive disease: epidemiological data

Claudio Borghi
University of Bologna, Bologna, Italy

The demonstration that elevated levels of serum uric acid (SUA) can increase the risk of cardiovascular disease requires a mechanistic interpretation of the possible role of additional risk factors that might promote such a deleterious association. Among them, arterial hypertension (HTN) is playing the most relevant role and s strict relationship has been repeatedly described between elevates levels of SUA and the progressive increase in blood pressure values. All these evidence support a possible role of serum uric acid as an independent risk factor for cardiovascular disease and suggest the importance of a more extensive investigation with the aim to increase the possibility of effectively reduce the impressive burden of cardiovascular diseases. A direct association between SUA levels and HTN has been described in animal models where a progressive increase in blood pressure values can by induced by increasing the plasma levels of uric acid. Conversely such a inducible blood pressure response can be entirely prevented by the pharmacological blockade of uric acid production with a xantino-oxidase inhibitor as febuxostat. In humans the relationship between SUA and hypertension is already evident in the pediatric as well as in the adolescent population where the average blood pressure values are reported to be significantly elevated in presence of increased SUA levels. These observations support the challenging hypothesis that the increase in serum uric acid levels can antedate the development of hypertension and can play a patogenetic role in the development of cardiovascular disease by promoting vascular abnormalities leading to a worsen blood pressure control. The sequential progression from hyperuricemia to hypertension is also supported by the results of a pivotal observational study, the Bogalusa Heart Study, where a significant correlation has been found between the plasma levels of UA during the adolescence and the

systolic and diastolic blood pressure values recorded 20 years later during the adulthood.

In particular the condition of oxidative stress associated with the activity of xantino-oxidase that is involved in the production of uric acid, is leading to a reduced endothelium-dependent vasodilating response as well as to an increase in renal vascular resistance. The systemic vascular involvement contributes to an increase in total peripheral vascular resistance while the renal vascostrictive response is associated with an exaggerated salt-sentitivity that is resulting in a volume-dependent hypertension that persist when the sensitivity to salt intake is returned to the baseline levels. The progressive nature of the link between SUA and hypertension clearly support the possibility of a prevention of the hypertensive disease in subjects with hyperuricemia. In particular any possible strategy aimed at controlling the plasma levels of SUA, particularly in the younger population (e.g. reducing the ingestion of fructose-added beverages, beer, etc) might prevent the blood pressure increase and the future development of hypertension. In adolescent subjects with SUA levels outside the normal range, the administration of the non selective xantine-oxidase modulator allopurinol has been associated with a significant decrease of both systolic and diastolic blood pressure values and this has been confirmed in patients with mild hypertension where the plasma levels of SUA are usually not considered in the management of the hypertensive disease. More recently some interesting evidence has been provided supporting the possibility that the presence of elevated levels of SUA can significantly reduce the efficacy of the antihypertensive treatment with a worst blood pressure control in patients with uric acid levels outside the normal. These might explain the observation that the prevalence of hyperuricemia is directly correlated with the degree of severity of the hypertensive disease in the general population where the extent of blood pressure control is the final result of the interaction between the mechanism promotig the blood pressure increase and the individual efficacy of the antihypertensive treatment.

All the above information clearly support a massive effect of serum uric acid on blood pressure control in humans and identify the management of hyperuricemia as one of the future strategies for the prevention of hypertension and correlated cardiovascular disease.

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Uric Acid and Blood Pressure Profile

Guido Grassi
Clinica Medica, Università Milano-Bicocca, Ospedale San Gerardo, Monza, Milano, Italy

Serum uric acid has been associated with an increased cardiovascular risk, but no conclusive evidence exists on whether it is an independent risk factor or a reflection of other risk factors to which it is related. We examined the possible relationships of serum uric acid with a number of cardiovascular variables [including risk factors never evaluated before, such as organ damage and out-of-office blood pressure (BP)], as well as its prognostic relevance in the population. In 2045 participants of the Pressioni Arteriose Monitorate E Loro Associazioni study, we measured, along with left-ventricular mass index, and office, home and ambulatory BP. Cardiovascular and all-cause mortality was assessed over a 16-year follow-up period, and measurements were repeated 10 years after the initial data collection. The results showed that baseline SUA had a near-normal distribution, with a mean value of 4.9±1.3 (standard deviation) mg/dl and a significant direct relationship with blood presssure and metabolic variables, serum creatinine and left ventricular mass index. It was among the factors independently predicting new-onset home and ambulatory hypertension, the increased risk of developing these conditions for 1 mg/dl increase of serum uric acid after adjustment for all available potential confounders being 34 and 29%, respectively (P=0.015 and P=0.014). An increase in serum uric acid of 1 mg/dl also independently predicted cardiovascular and all-cause mortality, the fully adjusted increase in risk being 22% (P=0.03) and 12% (P.0.04), respectively. Thus, in the general population of the Pressioni Arteriose Monitorate E Loro Associazioni study, serum uric acid correlated with a number of cardiovascular risk factors. Nevertheless, it independently predicts new-onset out-ofoffice hypertension, and long-term cardiovascular and all-cause mortality.

Management of serum uric acid and prevention of hypertension

Renata Cífková
Center for Cardiovascular Prevention, Charles University in Prague, First Faculty of Medicine and Thomayer Hospital, Prague, Czech Republic

In recent years, uric acid has been proposed to have a causal role in some forms of hypertension.[1] For quite a long time, this association was attributed to the effect of renal vasoconstriction to reduce the urinary excretion of uric acid. More recently, uric acid seems to have a causal role in hypertension, particularly in early hypertension.[2]

Animal models suggest uric acid induces hypertension by a two-step process starting with renin-mediated vasoconstriction followed by arteriolopathy that causes a sodium-sensitive phenotype. Increases in serum uric acid in experiment result in hypertension with a blood pressure (BP) increase proportional to that of uric acid. Early hypertension is reversible with uric acid reduction, but prolonged hyperuricemia results in irreversible sodium-sensitive hypertension that becomes uric acid-independent.

Epidemiological studies link hyperuricemia to present and future hypertension. Increased uric acid can result from decreased renal function and, in general, chronic kidney disease (CKD) results in higher serum uric acid. The largest effect of serum uric acid on CKD risk was seen in the Okinawa Health Study, in which serum uric acid of more than 8 mg/dl was associated with a threefold increase in the risk of developing hypertension. There are five additional studies demonstrating an association between uric acid and progressive decline in renal function. Population studies have shown that the incidence of hypertension increases in a continuous and graded fashion with increasing quartiles of serum uric acid.[3] The strongest association of uric acid with hypertension is with new-onset essential hypertension.[4]

The relationship of uric acid with systolic BP in control subjects and in subjects with primary hypertension was continuous and strong ($r = 0.8$; $p < 0.001$) and cannot be explained by obesity or decreased renal function. Interestingly, the association between hypertension and serum uric acid is less strong in adults. This suggests that an elevation in uric acid may be more important in the development of hypertension than its maintenance.[5]

Experimental evidence in humans

1. **Pilot study**

   An open-label pilot study in five adolescents with newly diagnosed hypertension was performed. Study subjects were treated with allopurinol (200 mg twice daily) for 1 month followed by a 4-week washout period. Reduction of serum uric acid levels from 6.9 ± 0.6 to 3.3 ± 0.4 mg/dl ($p < 0.0005$) was associated with a significant reduction of casual systolic BP (from 140.0 ± 3.6 to 131.2 ± 6.1 mmHg; $p < 0.017$) verified by ambulatory BP monitoring (normalization of BP in four of the five subjects).[6]

2. **Randomized trial (crossover design)**

   A total of 30 adolescents (aged 11 to 17 years) with newly diagnosed, never treated stage 1 essential hypertension and serum uric acid ≥ 6 mg/dl were randomized to receive allopurinol (200 mg twice daily) or placebo for 4 weeks, with a 2-week washout period between treatments. Treatment with allopurinol resulted in a significant reduction of casual BP (allopurinol: –6.9/–5.1 vs placebo: –2.0/–2.4 mmHg) and mean ambulatory BP (allopurinol: –6.3/–4.6 vs placebo: 0.8/–0.3 mmHg). Blood pressure normalized in 20 out of the 30 participants during the allopurinol phase.[7]

3. **Follow-up clinical trial (7-week active treatment followed by 4-week washout and follow-up)**

   A total of 60 obese children with prehypertension were randomized into 3 groups to receive placebo, allopurinol, and probenecid for 7 weeks. Patients in the active treatment groups experienced a marked reduction in office BP (allopurinol: –10.1/–8.0 mmHg; probenecid: –10.2/–8.8 mmHg) and 24-hour ABPM.[8]

These data confirm that the mechanism of BP lowering is uric acid reduction and the effects can be demonstrated in children with prehypertension as well as in stage 1 hypertension. Despite the utility of uric acid lowering for BP reduction in children with elevated uric acid, allopurinol is currently not recommended for initial therapy of essential hypertension for the following reasons:

1. The efficacy needs to be confirmed in larger trials with broader populations.
2. Allopurinol and probenecid have inferior adverse effect profiles in comparison with conventional antihypertensive medication. Allopurinol can cause a rare but life-threatening reaction known as allopurinol hypersensitivity syndrome characterized by rash, impaired renal function, hepatocellular injury, fever, eosinophilia, and leukocytosis. Probenecid alters renal clearance of numerous drugs and may induce nephrolithiasis in the setting of hyperuricemia.

Despite these limitations, there is an appeal to treat hyperuricemia as the underlying mechanism of hypertension as well as the possibility of preventing vascular change that results in irreversible disease by requiring further studies and development of new uric acid-lowering agents. Currently, there are some available alternatives: (a) losartan, an angiotensin-receptor blocker with mild uricosuric properties, and (b) febuxostat, a new non-purine xanthine oxidase inhibitor formally not tested yet in this indication.

Conclusions

There is strong evidence linking elevated serum uric acid to essential hypertension, making hyperuricemia a reasonable biomarker for diagnosis. However, further research needs to be completed prior to initiating treatments for hypertension aimed at uric acid reduction.

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Uric acid, gout and CV disease: which evidence?

Austin Stack
Department of Nephrology, University Hospital Limerick, Limerick, Ireland

Despite an accumulating body of evidence linking gout with adverse cardiovascular outcomes, there remains continuing doubt as to whether hyperuricaemia can be truly considered an independent major cardiovascular risk factor. Much of this doubt stems from the fact that many patients with gout who develop major cardiovascular events are also burdened with co-existing cardiovascular risk factors thereby potentially confounding any relationship between gout and adverse cardiovascular events. Furthermore, conclusive evidence from large randomised clinical trials linking better outcomes with lowering of uric acid levels is unavailable. This lack of convincing evidence is obvious to the wider clinical community and this gap in our knowledge needs to be addressed by the scientific community in a rigorous and robust manner.

The goal of this presentation is to examine the published scientific literature and determine whether there is sufficient biological, epidemiological and clinical trial data that would support the presence of a causal relationship between gout and major cardiovascular events. In establishing causality, consideration will be give to both direct and indirect mechanisms through which hyperuricaemia and gout may contribute to excess cardiovascular events. There is strong biological evidence that links hyperuricaemia with endothelial dysfunction, inflammation, oxidative stress and activation of the renin angiotensin system. These pathophysiologic processes lead to a definite renal arteriopathy and the development of hypertension, both of which are considered risk factors for cardiovascular disease.
While it is possible that a single pathway exists through which uric acid leads to cardiovascular disease; it is more plausible that the multiple pathways are involved which converge to amplify the downstream risk of

major cardiovascular consequences. Several recent metaanalyses, have identified strong associations between uric acid and the development of hypertension, Type 2 diabetes, metabolic syndrome and chronic kidney disease, each of which are well established risk factors in their own right for total and cardiovascular mortality. It is tempting to speculate that the development of these conditions are the "true intermediaries" in the causal pathway and may reflect the multiple mechanisms through which uric acids exerts its influence on the development of cardiovascular disease.

The weakness of the existing causality framework is the obvious lack of definitive intervention studies to test the effect of urate lowering agents on reducing cardiovascular events. In their absence, efforts have concentrated on using linked databases and real-world clinical cohorts to explore the benefits of urate lowering therapies on reducing major cardiovascular. Although information is emerging that urate lowering is linked to improved cardiovascular outcomes, more compelling and consistent evidence from scientific studies is warranted to prompt a change in clinical guidelines and convince the wider clinical community.

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The mechanisms of vascular involvement in patients with hyperuricemia

Stefano Taddei
University of Pisa, Italy

Uric acid has been associated by many epidemiological studies to increased incidence of cardiovascular events[1]. Though the pathogenetic link has not been fully demonstrated yet, increasing experimental and clinical evidence suggests that this deleterious effects occur mainly at the vascular level [2]. Xanthine oxidase, the enzyme involved in purine catabolism and involved in production of uric acid from hypoxanthine, has been recognized as one of the main sources of oxidative stress within the endothelial cells: this phenomenon is responsible for reduction in endothelial nitric oxide availability, defining so the presence of endothelial dysfunction [2]. High levels of uric acid have been also associated with low-grade inflammatory state and vascular renin-angiotensin system activation [3,4]. These changes might promote accelerated atherosclerosis, thus increasing cardiovascular risk. In a big cohort of middle-aged healthy Japanese men, not only severe, but also mild hyperuricemia appeared to be a significant independent risk factor for endothelial dysfunction, measured by flow-mediated dilation [5]. In a study conducted in 217 patients with uncomplicated hypertension, endothelial function was studied by forearm pletismography after intrarterial administration of acetylcholine: in this study serum uric acid was inversely associated with endothelial function independently of other cardiovascular risk factors [6]. Furthermore, high levels of serum uric acid have been associated with an increased risk for hypertension onset[7]. Treatment with xanthine oxidase inhibitors is able to restore endothelial function in patients with hyperucemia at high cardiovascular risk, but not in patients with normal serum uric acid levels [8]. Other studies suggests that the restoration of endothelial function by drugs inhibiting xanthine oxidase is due to oxidative stress reduction rather than to serum uric acid lowering [9].

Furthermore. hyperuricemia is also associated with several cardiovascular risk factors, and in particular with metabolic syndrome [10], which are per se associated with endothelial dysfunction. Thus is difficult to establish whether the association between uric acid and endothelial dysfunction is an independent one.

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Serum uric acid and atrial fibrillation: epidemiology and mechanism of disease

Athanasios J. Manolis
Cardiology Department, Asklepeion Hospital, Athens, Greece

Atrial fibrillation is the most common arrhythmia in the USA, Europe and other developed countries, accounting for one third of all patient discharges with arrhythmia as a principal diagnosis. The overall incidence of atrial fibrillation increases with each decade of age, affecting nearly 6 % of people over age 65 years, 15 % of people over 80 years, and its prevalence is expected to at least double in the next 50 years as the population ages. Different risk factors, subclinical and clinical organ damage such as age, hypertension, diabetes mellitus, obesity, obstructive sleep apnoea, left ventricular hypertrophy, coronary artery disease, heart failure and others contribute to the development of atrial fibrillation. Serum uric acid, the final product of purine metabolism catalyzed by xanthine oxidase, has been reported to be positive correlated with hypertension, metabolic, syndrome, kidney and cardiovascular disease. Several observational studies have shown that high uric acid predicts the incidence rate of hypertension in population based studies. Hypertension is the most common cardiovascular disorder and atrial fibrillation is the most common clinically significant arrhythmia. Both these conditions frequently coexist and their prevalence increases rapidly with aging. There are different risk factors and clinical conditions predisposing to the development of atrial fibrillation, but due its high prevalence, hypertension is still the main risk factor for the development of atrial fibrillation. The relationship of uric acid with hypertension and cardiovascular complications is remarkably strong in women and in patients at high risk for cardiac and arterial complications.
Recently accumulative evidence suggest that there is an association between increased levels of uric acid and atrial fibrillation.

Regardless of the debate as to whether uric acid it is a predictor or a causative factor, uric acid has been clearly associated with oxidative stress and inflammation in several conditions. In particular, inflammatory indices, mainly CRP, but also interleukin-6, and tumor necrosis factor have been related to future atrial fibrillation development, persistence, recurrence, and left atrium enlargement. The same time CRP and interleukin-6 are related to higher uric acid levels. Recent studies have shown that 1. Elevated serum uric acid was associated with an increase systemic inflammation, insulin resistance and decreased eGFR 2. Serum uric acid was positively correlated with left atrium size 3. Hyperuricemia was a risk factor for the occurrence of atrial fibrillation 4. The severity of gout had a significant effect on left ventricular diastolic dysfunction and left atrial enlragement in gout patients 5. Elevated serum uric acid levels are strongly associated with increased incidence of atrial fibrillation in patients with type 2 diabetes mellitus 6. The occurrence of atrial fibrillation in obstructive sleep apnoea patients is strongly related to serum uric acid levels, left atrium diameter, percentage of time with SaO2<90% and CRP levels.

Whether treatment of hyperuricemia will prevent the development or recurrence of atrial fibrillation is a topic for future research.

Hyperuricemia and CV disease: the role of renal impairment

Eberhard Ritz
Department of Nephrology, Nierenzentrum, Heidelberg, Germany

Hyperuricemia predisposes to cardiovascular disease as well as to renal impairment; the presence of renal impairment amplifies the adverse impact of uric acid on cardiovascular disease.
In animals uric acid provokes transformation of renal tubular epithelial cells into fibroblasts and provokes inflammatory reactions *(Ryu, Am.J.Physiol.(2013)304.F432)*. Uric acid triggers in the kidney as well as in the heart endothelial dysfunction, inflammation, oxidative stress etc…
In patients with gout plus CKD the risk of death from CV disease is particularly increased *(Kok, BMC (2012) 12:108)*.
Even in the absence of gout the particularly adverse outcomes in patients with the triple constellation cardiac disease, high serum uric acid and reduced GFR have been documented in several clinical studies *(Nutrition Metabolism Cardiovascular Diseases (2013) 23:46)*. Even in the absence of cardiac disease the prognosis is adverse for patients with the triangular constellation of higher serum uric acid, reduced renal function and hypertension *(Silbernagel,Nutr.Metab.CVD(2013) 23:46; Jalal AJKD(2012)61:134)*.
In patients with primary kidney disease hyperuricemia predisposes to more rapid impairment of renal function, as documented in IgA-glomerulonephritis *(Kohagura, Hypertension Research (2013) 36:43)* as well as in diabetes and diabetic nephropathy *(Zoppini, Diab.Care (2012)35:99)*.
Even in isolated kidney disease the serum uric acid concentration is an independent predictor of more rapid loss of GFR and a higher risk of CV events *(Kanbay, American Journal Nephrology (2012) 36: 324)*.
Lowering serum uric acid concentrations attenuates progression of renal lesions and renal function loss: this had been documented first with Allopurinol *(Goicoechea, CJASN (2010) 5:1388)* as well as more recently with the more powerful Febuxostat *(Sezai, Circulation Journal (2013)*

77:2043); these intervention trials have also documented that in CKD patients lowering of the s-uric acid concentration reduces GFR loss as well as the frequency of cardiac complications and CV events *(Ito, Hypertension Research (2012) 35:867).*

Early treatment with uric acid lowering is important because advanced lesions are more resistant to treatment *(Mazzali, AJPR (2002) 282:F991).*

Is there anything good in uric acid?

Alberto Morganti
U.O. di Medicina Interna, Centro Ipertensione Arteriosa, Ospedale San Giuseppe, Università di Milano, Milan, Italy

Uric acid (UA) is an organic compound and a potent reducing agent that represents the end product of purine catabolism in higher primates and humans. Several lines of evidence indicate that high levels of UA are a risk factor for cardiovascular diseases, hypertension, renal diseases, diabetes and stroke. However UA may exert favourable effects as well. For instance epidemiological studies have associated low levels of UA in plasma to some neurodegenerative diseases, like Alzheimer and Parkinson diseases and multiple sclerosis (1). This neuroprotective effect of UA is usually attributed to the antioxidant action of this compound in the central nervous system (CNS) but until recently the precise mechanism was unclear.

Recent studies in animals have shown that UA like caffeine, an other purine derivative, increases glutathione synthesis; glutathione, in turn, is the most relevant thiol reducing agent that exerts major anti-oxidant effects in the CNS (2). In addition in CNS UA increases cysteine uptake, the main regulator of neuronal glutathione synthesis. Moreover in slice culture experiments hippocampal neurons treated with allopurinol, an inhibitor of UA production, were resistant to oxidant exposure. It is of interest that these neuroprotective effects were exerted in the brain at concentration lower than in blood.

UA may also have a protective role against the aging process. The rise in UA associated with the loss of uricase, the enzyme which oxidizes UA to allantoin in lower species, may protect against oxidative stress and prolong life time (3).

Another area where UA may have beneficial effects is the acute ischemic stroke (AIS). In animal models and in humans high levels of UA are independent prognostic factor of better outcome after AIS (4) and may enhance the benefits of thrombolysis.

In a recent study carried out in 1336 patients with AIS treated with thrombolysis within 3 hours after the onset of symptoms, the short term clinical improvement was greater in subjects with high UA levels at admission (5). Also after the statistical adjustment for possible confounders UA was positively correlated with clinical improvement and was an independent predictor of favourable outcome. This finding goes along with that of Amaro and coworkers (6) who showed that in patients undergoing thrombolysis for AIS those with higher values of UA had smaller infarct volume.

It is likely that under the conditions of an excess oxidative stress, further reinforced by the burst of reactive oxygen species occurring during early tissue reperfusion, UA may act as a antioxidant agent scavanging the oxidant substances and preventing neuronal death.

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Serum uric acid, stroke and cognitive function

Daniela Mastroiacovo[1], Antonio Camerota[1], Anna Maria Stati[1], Giovambattista Desideri[1].
[1]*Geriatric Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy*

Dementia represents a prominent issue in global healthcare due to its great impact on quality of life of patients and caregivers and a so great prevalence that is assuming the characteristics of a real epidemic. Moreover dementia is going to increase further in the coming years due to the progressing aging of the population and consequent increasing of the age group in which dementia is more common (1). Clinical course of dementia is inevitably progressive and over a period of time, ranging from few months to few years, it leads to a severe deterioration of personality and social life of patients who become totally dependents on caregivers. Nowadays, a great attention is being rewarded to the identification of the causes and the pathophysiological mechanisms underlying cognitive deterioration and dementia. A growing interest has been directed mainly to the role of vascular and inflammatory factors in the onset and progression of cognitive impairment (2-4). In this regard, during the last few years growing scientific evidence have suggested the existence of a close relationship between circulating levels of uric acid and biomarkers of systemic inflammation (5). Furthermore hyperuricemia is a risk factor for hypertension, diabetes, metabolic syndrome, endothelial dysfunction, cardiovascular and cerebrovascular diseases (6-9). Therefore, it is not surprising that some interesting scientific evidences suggested a "dangerous relationship" between serum uric acid levels and cognitive functions, providing evidence of an association between the increased circulating levels of this purine metabolism product and the risk of vascular cognitive impairment and small vessels disease.
An interesting study from Schretlen et al. (10) described an increased risk of worse results in tests investigating executive functions such as processing speed, verbal memory, and working memory among elderly

resident in nursing home with moderate elevation of uric acid levels. The risk remained significantly increased even after correction for potential confounders including age, race, education, diabetes, hypertension, smoking, and alcohol abuse. Similarly, in patients with chronic kidney disease, defined by a glomerular filtration rate <60 mL/min/1.73 m^2, an independent association between circulating levels of uric acid and reduced cognitive performances has been described (r: -0.297, p <0.0001) (11). In accordance with this evidence in the InChianti study, which cross-sectionally assessed the relationship between circulating levels of uric acid and the risk of dementia in 1016 community-dwelling elderly subjects, demonstrated higher circulating levels of uric acid (5.75 ± 1.90 vs 5.13 ± 1.35 mg / dL, p <0.001) in patients with dementia and an increased prevalence of dementia cases in the highest tertile of serum uric acid (12). Even after adjustment for the possible confounding factors, the highest tertile of serum uric acid was associated with a threefold risk of dementia (OR= 3.32, 95% CI:1.06 –10.42), while the intermediate tertile was associated with a higher probability of dementia than the lowest tertile. It is interesting to observe that the relationship between circulating levels of uric acid and dementia remained significant even after adjustment for possible confounding factors and that it was already evident for levels of uric acid substantially within the normal range (12). In contrast, at least apparently, with these evidence, some studies do not seem to support the hypothesis of a harmfulness of the uric acid with regard to the cognitive functions. The levels of uric acid, for example, tend to be lower in patients with Alzheimer's disease or overt vascular dementia (13-15). Some evidences also suggest the possibility that increased circulating levels of uric acid in patients with initial cognitive impairment could reduce the risk of progression to dementia (16). Furthermore, the impact of uric acid on the risk of dementia would tend to disappear and to be replaced by a protective effect even after adjustment for possible comorbidities such as hypertension and cerebrovascular disease (17).

These discrepancies among the various scientific evidence are probably due to differences in the enrolled populations in the several studies and

the different degree of adjustment for the potential confounding factors. It should also be considered that the circulating levels of uric acid gives an indication, although approximately, on the nutritional status of the patient. The reduced circulating levels of uric acid in patients with dementia may, therefore, reflect a state of malnutrition which could also facilitate the progression of cognitive impairment independently on to the circulating levels of uric acid. Reduced plasma concentrations of uric acid may also reflect a decrease in the antioxidant defences, a condition for which it has been hypothesized for long time a pathogenic role in Alzheimer's disease (13-15). Nevertheless, the scientific evidence seem to suggest a negative influential role of circulating uric acid on cognitive function which seems to occur independently on urate crystal precipation since it is evident for serum uric acid levels below the saturation threshold of 6 mg/dL. In this regard, uric acid seem to have all the biological potential to affect cognition mainly because it is able to impair brain perfusion due to its ability to promote vascular dysfunction and damage which can promote neurodegeneration (6,7). In addition, increased circulating levels of uric acid are associated with an increased risk of stroke (18) which, in turn, increases the risk of developing vascular dementia and accelerates the progression of cognitive impairment in Alzheimer's disease (19). Increased oxidative stress has been also proposed as potential determinant of cognitive impairment in hyperuricemic subjects (20). Indeed, the well known antioxidant effect of uric acid gradually diminishes with the increase of its concentration in biological fluids up to be converted in a prooxidant effect for concentrations >6mg/dL (21). In addition, it worth to be mentioned that the enzymatic activity of xanthine oxidase, which generates uric acid, represents a relevant source of oxidative stress (22). According to this, an increase in the activity of the xanthine oxidase has been demonstrated in tissue sections from atherosclerotic plaques (23). Finally, the ability of serum uric acid to promote a chronic systemic inflammation should be also considered to explain the detrimental influence of serum uric acid on cognitive function (24,25).

Indeed, urates are able to stimulate the production of angiotensin II, thromboxane, interleukin-1β, interleukin-6 and tumour necrosis factor-α (20,24-26). In conclusions, the evidences of the scientific literature suggest the possible involvement of uric acid in the pathogenesis of cognitive impairment and dementia. This “dangerous relationship" between uric acid and cognitive function seems to manifest itself also for normal-high concentrations of this end product of purine metabolism, in accordance with what was observed with the other "dangerous relationship" between uric acid and cardiovascular disease. The biological plausibility of the hypothesis that uric acid can promote the development of cognitive impairment through many pathophysiological mechanisms further supports the epidemiological evidence of a tight association between serum uric acid and cognitive dysfunction. It remains to be defined whether the reduction in circulating levels of uric acid can result in a reduction of the risk of developing dementia or it can slow the progression of early cognitive impairment.

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Can we affect the CV diseases by managing serum uric acid?

Daniel Feig
Professor of Pediatrics, Division of Nephrology, University of Alabama, Birmingham School of Medicine, Birmingham, AL, USA

The possibility that serum uric acid is a mediator of hypertension and or more general cardiovascular disease has been controversial for more than 130 years. Frederick Mahomed originally proposed that uric acid causes high blood pressure in 1879 and Alexander Haig followed up by hypothesizing that uric acid had wide ranging deleterious effects on vasculature, myocardium, kidneys, liver and immune system. Cardiovascular epidemiology studies have consistently identified elevated uric acid as a risk factor for hypertension and cardiovascular mortality; however, in some, multiple regression, particularly for hypertension and renal disease, have muted the apparent effect, casting doubt on whether uric acid is a mediator of CV disease. In the United States, during the 1970s and early 1980s, treatment of ”asymptomatic hyperuricemia” was relatively common. At the time there were no studies on the CV impact of such therapy but a significant number of severe allopurinol associated adverse drug reactions, including Steven Johnson Syndrome, led to strong recommendations not to treat or even to screen for isolated hyperuricema. Between 1998 and 2005, Johnson and colleagues performed a series of animal model experiments that indicated that increased serum uric acid led directly to hypertension and vascular injury. These experiments suggest uric acid causes hypertension by a 2-step process. Initially, uric acid uptake into vascular endothelial cells causes acute activation of the renin angiotensin system and decreased vascular NO elaboration which result in vasoconstriction and increased BP. If hyperuricemia resolves, or is treated, vascular tone and BP return to normal. Over extended periods of hyperuricemia, uric acid induces vascular smooth muscle proliferation and reduced vascular compliance which result in Sodium sensitive hypertension that is irreversible.

If the animal data predict human physiology, patients with long term hyperuricemia would be expected to have hypertension that is less responsive to urate lowering therapy but early uric acid mediated hypertension might be curable. Based on this hypothesis, our group performed an initial trial of urate lowering therapy on adolescents with newly diagnosed essential hypertension who also had serum uric acid levels >6.0mg/dL. Thirty children were randomized to allopurinol or placebo for 4 weeks followed by a 2 week washout then a 4 week crossover. While on allopurinol 22 of 30 patients normalized their blood pressure compared to 1 of 30 on placebo. The mean fall in SBP was 7mm Hg on allopurinol compared to 2mm Hg on placebo. In a follow up study of adolescents with obesity, prehypertension and elevated uric acid, 60 patients were randomized to allopurinol, probenecid or placebo. Patients on urate lowering therapy had a mean decrease in SBP of 10mm Hg over the 2 month treatment period, whereas patients on placebo had a small increase in SBP. Assadi and colleagues randomized 44 adolescent patients being treated for hypertension with the ACE inhibitor enalapril and had serum uric acid >5.5mg/dL to placebo versus allopurinol. Patients receiving allopurinol has significantly greater fall in BP.

There are currently no published randomized controlled trials testing the use of urate lowering therapy for blood pressure control in adults. The SURPHER (**S**erum **U**ric acid **R**eduction to **P**revent **H**y**PER**tension) which is currently enrolling subjects, will test the hypothesis that uric acid reduction with allopurinol will reduce blood pressure and systemic inflammation in young adult patients but results are not expected until 2016. In gout control studies, all performed in adults, when blood pressure has been assessed in post hoc analysis, the impact of xanthine oxidase inhibition on BP has been variable. In the PREMIER trial, of nonpharmacologic therapy for hypertension, diet and exercise interventions were highly effective but the patients who had the greatest reduction in uric acid also tended to have the greatest reduction in blood pressure.

The paucity of adult data has been emphasized in recent meta-analyses published in the Journal of Clinical Hypertension and Cochrane Reviews which both indicate modest preliminary data to suggest that uric acid reduction might hold some promise for hypertension and CV risk mitigation, the currently published data are insufficient to support mainstream therapy.

The animal model data and clinical trials in adolescent patients indicate promise for urate lowering therapy in the prevention of chronic hypertension and reduction of CV disease risk. Definitive clinical trials are sorely needed.

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