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URIC ACID, GOUT AND BEYOND: IS CV RISK A NEW OBJECTIVE?

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ABSTRACT BOOK

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Serum Uric Acid and cardiovascular risk: facts and fiction

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Abstract

Hippocrates described the cardiovascular consequences of podogra more than 2 Millennia ago. Although likely bemused to see the same issue addressed here in 21st Century Italy, he would surely be pleased that the story of Gout, Uric Acid, and cardiovascular disease continues to capture the attention and imagination of the biomedical community.

The modern era can be said to have begun with the 1897 Presidential Address to the American Medical Association, Nathan Smith Davis postulated that high blood pressure might be due to the toxic effects of Uric Acid which, in turn, could be responsible for much renal damage. Then, in 1951, Menard Gertler and Samuel Levine reported that patients, hospitalized with coronary artery disease, had higher serum Uric Acid than comparable patients without. Clinical and Epidemiological studies subsequently demonstrated the high prevalence of "elevated" Uric Acid, as well as the important variation across national boundaries, according to drug use, between sexes, and in association with various metabolic and cardiovascular conditions. Moreover, several studies demonstrated that increasing Uric Acid was associated with cardiovascular-renal disease. Dissenting views not withstanding, a consensus that Uric Acid is a risk factor for cardiovascular disease seems to have emerged.

During the past several decades, the molecular biology of Uric Acid has also been elucidated, and drugs that either mute production, or increase Uric Acid excretion are being tested to determine their for potential cardiovascular benefit. Finally, an animal model of mild hyperuricemia has been created. Still, despite these remarkable advances, the daunting issues of causality and reversibility remain.

Hopefully, the remarkable confluence of experience, knowledge, and imagination present at this conference will bring closer the translation of possibility into practical human benefit.

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The epidemiology of hyperuricemia and gout

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Accumulating data support an increase in the prevalence of gout that is potentially attributable to recent shifts in diet and lifestyle, improved medical care, and increased longevity (1). In England, the prevalence of gout increased from 0·3% to 1% between 1970 and 1990 (2) and a similar trend was observed in the United States during the 1990s, especially for men older than 75 years, in whom the prevalence of gout nearly doubled, from 2·1% in 1990 to 4·1% in 1999 (3). More recently, the prevalence of gout among US men in 2007–2008 was computed as 5.9% (4). The prevalence of gout from 2000 to 2005 has been estimated at 1·4% in the United Kingdom (5). Gout seems to be the most prevalent inflammatory arthritis disease in Western countries, especially in elderly men. Gout has also become frequent in other parts of the world, such as China, Polynesia, New Zealand and urban sub-Saharian Africa. In New Zealand, the increase has been even greater in the Maori population than in the European population. In 1992, in Maori subjects, the prevalence of gout, not recognized prior to Western colonisation, was 6·4% (6). In Eastern China, where the disease was unknown in 1980, the prevalence was recently estimated at 1·14%, following changes in lifestyle and dietary behaviour (7).

Gout prevalence is much higher in men and increases with age. Gout in women mainly develops after menopause: the decreased level of estrogen, which is uricosuric, increases uricemia. Postmenopausal hormone use is associated with lower uricemia (8). Alcohol and dietary excess have long been associated with gout. The incidence of gout increases with high consumption of meat, seafood, and fructose, and intake of beer and spirits. Vegetables with a high purine content and moderate wine drinking had no effect on the incidence (9, 10). The incidence of gout increased as well with increased body mass index but decreased with loss of weight (11). Consumption of dairy products, vitamin C and coffee, including decaffeinated coffee, is

associated with decreased uricemia or incidence of gout, or both (10, 12, 13).

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Updated Recommendations for the Diagnosis of Gout and Hyperuricemia

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Gout is the most frequent chronic inflammatory arthritis in men and an increasing cause of arthritis in women (1,2). Despite this high frequency and the availability of effective drugs, studies reveal that only a minority of gout patients receive appropriate treatment and adequate information about the disease (3-5). Although the raisons for this poor approach to the gout are not easy to explain, it is possible that the basic defect is cultural (6). In undergraduate medical curricula and general practitioners (GPs) training programmes, musculoskeletal conditions and in particular gout, have low prioritization (5-7). In addition, because gout is not a hospital-based disease, resident doctors' exposure to gout and their experience of gout management is limited (5-7). Since gout is most often diagnosed and managed by GPs, it is possible that their insufficient knowledge of the disease in general and of existing recommendations in particular, may contribute at least in part to this inappropriate management of gout observable in real life (5-7).

The 2006 European League Against Rheumatism (EULAR) evidence-based recommendations on gout were elaborated with the aim to satisfy most of these needs and still represent an important hallmark in field of gout (8). As regard the diagnostic aspects, recommendations underlined that, although diagnosis of typical acute attacks of gout is possible from the clinical features alone, less typical presentations require confirmation of crystal presence in joint or tophus aspirates (8). However, joint aspiration and subsequent synovial fluid (SF) analysis to detect monosodium urate (MSU) crystals is often not performed, not only by GPs but even by most specialists involved in the management of musculoskeletal diseases. So, the routine demonstration at microscope of MSU for the diagnosis of gout may not be feasible in practice due to the difficulty of locating a reference laboratory that can identify MSU correctly. This aspect may be

problematic also in the attempt to satisfy another important EULAR recommendation, suggesting that during the intercritical period, MSU crystals may be found in SF of affected joints even in asymptomatic patients (9). So, for most GPs, the diagnosis is usually based on a clinical history and serum uric acid (sUA) levels (5). Actually, sUA has limited diagnostic utility since levels can be normal during an acute flare and elevated in many patients who do not have gout but joint pain due to some other cause (8). However, in combination with clinical criteria, sUA can provide an additional indication that a patient may experience a gout attack and subsequently serve as a baseline value when monitoring treatment efficacy. Hyperuricemia may remain silent for years and does not always progress to clinically recognizable gout, but higher sUA levels are associated with a greater risk of gout.

Since 2006, when the EULAR recommendations have been published, new evidences from the research progresses for patients with gout have become available, for both the diagnosis and the management. So, there is a need to update these recommendations and many scientific societies, including the Italian Society of Rheumatology (SIR), are working on it to this aim.

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The inflammasome, uric acid and gout

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What is the inflammasome?

Inflammation is an essential defence mechanism for an organism to defend itself against external attack by microbes or by noxious substances. To coordinate our defences, the innate immune system plays a primary role, as it is the first line of defence. Over the last two decades, major advances have been made in the understanding of the mechanisms underlying innate immunity. Phagocytes are activated on contact with microbes and chemical agents through extracellular as well as intracellular receptors that trigger release of inflammatory cytokines and to modify cellular metabolism in a rapid response. One of the key cytokines in this reaction is IL1β, a pleiotropic cytokine that is released principally from monocytes, macrophages and dendritic cells. The production of IL-1β is tightly controlled on several levels. Transcription of IL1β mRNA is up regulated by many different stimuli, including the binding of ligands to TLRs and to the IL1R. The translated form of IL1β needs to be cleaved to generate the active 17-kDa form in order to signal through the IL1R. This "processing" requires the assembly of a cytoplasmic multiprotein complex that has been termed the inflammasome; responsible for the conversion of the zymogen procaspase-1 into the active caspase-1 that mediates IL-1β and IL-18 maturation [1]. Four major complexes activating caspase-1 have been described to date: the NLRP1, NLRP3, IPAF and AIM2 inflammasomes, amongst which the NLRP3 is best studied [2]. The NLRP3 inflammasome is composed of NLRP3 protein, an adapter ASC protein as well as the inflammatory caspase-1. The ASC adapter contains a PYD domain that mediates interaction with a homologous domain on NLRP, as well as a CARD domain that interacts with caspase-1. A large number of stimuli have been described to activate the NLRP3 inflammasome. These can be from bacterial origin such as muramyl dipeptide, bacterial RNA or double-stranded RNA or DAMPS (danger associated molecular patterns).

Crystals are potent inducers of IL1β

Microcrystals figure prominently among DAMPS that trigger the inflammasome. They include nanoparticles, alum, hemozoin, silica and cholesterol crystals, as well as crystals found in microcrystalline arthritis such as MSU, CPPD [3] and BCP crystals [4]. The steps that connect cellular contact of crystals and cytoplasmic inflammasome activation are still not completely understood. These steps may involve general mechanisms shared by other inflammasome activators, such as 1) the phagocytosis of crystals, 2) K^+ efflux that is regulated by K^+ channels like P2X7R, 3) sensing of reactive oxygen species (ROS) that are released during cell stress and 4) destabilization of the lysosomal membrane and activation of the lysosomal protease cathepsin B (see review in [5]). Two molecular pathways that may link certain DAMPs to NLRP3 activation have been identified, one through guanylate binding protein 5 (GBP5) and the other through via the thioredoxin-interacting protein (TXNIP) [6, 7]. However, they do not appear to be essential for microcrystal mediated inflammasome activation.

Recent data suggest that IL1a also participates in the response to microcrystals and that cooperation between IL1a and b secretion generates a maximal inflammatory response in vivo [8, 9].

Two signals are needed for full activation of the inflammasome

A major question that needs to be answered in pathological conditions such as gout is why is inflammation intermittent, even though crystals are present continuously. In laboratory studies, inflammation is only induced in animals when monocytes and macrophages are primed by another stimulus independent of the microcrystal. This priming or first signal could explain why inflammation in episodic. Priming signals that have been identified include ligands for TLRs such as LPS and CpG, and in vivo, long chain fatty acids have been found to be an effective priming signal in an animal model of gouty arthritis. These findings could explain why dietary or infectious triggers frequently precipitate acute gout.

Therapeutic implications

The key role of IL1(a and b) in inflammation triggered by microcrystals has been further confirmed by clinical studies employing IL1 inhibitors in the treatment or the prevention of acute gout. To date, three IL1 inhibitors have been used in clinical studies. Anakinra (IL1RA) inhibits both IL1a and b, as does rilonacept (IL1trap), whereas canakinumab specifically binds to IL1b. Clinical trials have tested these agents in either acute gout or in the prevention of acute attacks in patients who are initiating urate lowering therapy. All the studies published to date have shown positive results, and showed that IL1 inhibition is superior to either placebo or the comparator [10, 11]. At present, none of these drugs are licensed for the treatment of gout, though they have been approved for CAPS, an autoinflammatory disease that is due to mutations of the NLRP3-inflammasome. The safety as well as the cost benefit of these agents in the treatment of gout and other microcrystal diseases will have to be studied in the future.

Conclusions

The discovery of the inflammasome has provided a new paradigm to understand how acute and chronic inflammation is regulated in man. Gout is one of the first diseases to be linked with the NLRP3-inflammasome and has provided us with new insights of how the disease is triggered as well as opening up novel therapeutic approaches. The next decade promises to be an exciting one.

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How can uric acid promote gout and CV diseases? A biochemical point of view

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Uric acid has been associated epidemiologically with increased risk of cardiovascular (CV) morbidity and mortality, although the magnitude of excess risk seems to be small (1;2), the highest risk being observed in subjects with prevalent high CV risk (3). Although uric acid acts as a free radical scavenger, increased levels of uric acid have been associated to endothelial dysfunction, but the subjects' background and the range of hyperuricemia may also influence such relationship (4). Some have not found a direct association between urate and endothelial dysfunction, but an association with systemic inflammation (5). On the other hand, reduction of plasma urate levels has not clearly been associated with improved CV outcomes (6).

Presence of monosodium urate (MSU) crystals is associated with local inflammation and they activate the production of inflammatory cytokines through the NALP3 inflammasome (7). The presence of MSU crystals and subclinical inflammation in patients with longstanding hyperuricemia (8) may explain in part the link between hyperuricemia and CV events and why gout has been associated to the risk of CV events independently of the range of uricaemia (9).

Local increase of xanthine oxidoreductase (XO) in tissues may increase both urate and Reactive Oxigen Species (ROS) as a result of oxidative stress (10). Although this mechanism would not sufficiently explain hyperuricemia, as most patients show inefficient renal handling of urate, it would raise the benefits of including XO inhibitors as the cornerstone of urate-lowering treatment in patients with high CV risk (6).

Other mechanism cannot be overseen: patients may show hyperuricemia as an innocent bystander (11), current CV risk factors in the gout population (12), or even non-steroidal anti-inflammatory drugs (13), commonly prescribed to patients with gout, may influence CV outcomes.

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Uric acid, kidney function and the metabolic syndrome

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The pivotal role of the kidney in the disposal of uric acid is manifest by those diseases which specifically affect tubular function[1,2]. Invariably, tubular malfunction is followed by whole nephron failure. The converse is not necessarily true. Progressive kidney disease affecting glomerular function will ultimately affect uric acid excretion through loss of tubules but their potential to compensate for nephron loss by increasing secretion of urate illustrates the remarkable responsiveness of tubular transporters.

Nearly all subjects with gout exhibit a relative impairment of uric acid clearance which is dictated by genes[3]: clinical hyperuricemia develops when poor clearance is compounded by excessive stimulation of purine production and an increased uric acid load. This may be caused by alcohol ingestion or unknown mechanisms associated directly with body weight and to a less extent by diet.

A number of urate transporters have been identified on proximal tubules, the best known of which is GLUT9 which also transports fructose and glucose[5]. It is encoded by the gene SLC2A9, polymorphisms of which have been associated with a predisposition to gout in some European and Polynesian people[6]. The high prevalence of gout and hyperuricemia in Polynesians is linked to a pronounced impairment of urate clearance compared with their European counterparts[7]. However, it has not been possible to implicate variations of this gene with deficient urate clearance in any population group so far studied[8].

The first urate transporter to be identified was URAT1. This is encoded by the SLC22A1Z gene, mutations of which cause familial hypouricemia. Similar homozygous mutations of SLC2A9, the gene associated with the GLUT9 transporter result in more severe hypouricemia and greater hyperuricosuria and it is postulated that whereas URAT1 dysfunction causes a partial block of urate tubular

absorption, loss of the GLUT9 transporter results in total failure of the uric acid efflux across the tubular membrane.

Familial Juvenile Hyperuricemic Nephropathy (FJHN) when first described was thought to be a progressive kidney disorder of children and adolescents caused by precocious hyperuricemia[1]. Subsequently it has become clear that a) progression is the rule despite adequate hypouricemic treatment with allopurinol b) FJHN represents a group of linked disorders including medullary cystic kidney disease c) mutations of the uromodulin gene (UMOD) carried on chromosome 16p12 are common to at least three of these phenotypically similar disorders[9]. Uromodulin is found on the tubular cilia and in patients with mutations of UMOD is decreased. Other genetic abnormalities have been described in families with an FJHN like illness but and known genetic associations are as yet to be identified[10].
Thus in some instances, chronic kidney disease first affects that part of the proximal tubule responsible for urate transport. In many other diseases affecting kidney function, compensatory tubular mechanisms maintain urate homeostasis until late in the course of the illness. There is nevertheless an inverse correlation between serum urate levels and GFR in all populations and patients with a history of gout have an accentuation of age related decline in GFR[3]. Renal tubular handling of hydrogen ion and of urine concentrating ability deteriorate in parallel with GFR[11]. There is a strong association between hypertension and hyperuricemia and whether this is caused by alcohol excess, obesity or kidney disease itself can be difficult to ascertain in any individual patient. What can be certain is that uncontrolled hypertension will have an adverse impact on kidney function and this must account for some of the observed association of hyperuricemia with chronic kidney disease. Furthermore, the impact on the kidneys of repeated non steroidal anti-inflammatory drugs given for the acute arthritis of gout can only be speculated but is another likely contributor to renal damage.
A range of potential renal insults may thus have a cumulative impact on the kidneys in the hyperuricemic patient. A contentious and unresolved matter is whether hyperuricemia itself can be deleterious. The strongest case for this effect derives from a rat model in which

artificially induced hyperuricemia was followed by hypertension and interstitial renal disease[12]. There is limited evidence that treatment with hypouricemic drugs may delay the progression of renal dysfunction in gout[13,14].

Hypertension and obesity are probably relevant to the development of renal dysfunction in hyperuricemic subjects as discussed but do they imply that hyperuricemia is a feature of the metabolic syndrome? The latter is characterized by visceral obesity, insulin resistance causing type 2 diabetes and hypersecretion of very low density lipoproteins that lead to hypertriglyceridemia. There is an association between gout and hypertriglyceridemia that appears to be mediated by obesity and alcohol excess[15]. Blood glucose, triglyceride and uric acid levels do not have a direct impact on each other[16,17]. and the role of alcohol in this context is conceivably more important than obesity. Thus there is a relationship with the metabolic syndrome in those hyperuricemic subjects who are obese but this is not a constant amongst the hyperuricemic population nor is diabetes a regular concomitant of gout.

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Uric acid, gout and diabetes mellitus: a multifaceted connection

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The importance of hyperuricemia and the clustering phenomenon of the metabolic syndrome were first described by Kylin in 1923 when he described the clustering of three clinical syndromes: hypertension, hyperglycemia, and hyperuricemia. In 1988, Reaven GM described the important central role of insulin resistance in the seminal Banting lecture where he described Syndrome X, which has now become known as the metabolic syndrome (MS) and/or the insulin resistance syndrome (IRS). Seven decades after the clustering phenomenon was reported by Kylin, Reaven suggested that hyperuricemia be added to the cluster of metabolic and hemodynamic abnormalities associated with insulin resistance and/or hyperinsulinemia of Syndrome X (1).
The four major players in the MS are hyperinsulinemia, hypertension, hyperlipidemia, and hyperglycemia. Each member of this deadly quartet has been demonstrated to be an independent risk factor for CHD and capable of working together in a synergistic manner to accelerate both non-diabetic atherosclerosis and the atherosclerosis associated with MS, PD, and T2DM.
However, uric acid is not only a risk factor for type 2 diabetes and gout, but it is now recognised as a risk factor for diabetic long-term complications, in particular cardiovascular disease and renal disease.

Although the pathogenesis of diabetic nephropathy is complex and still not fully elucidated. Uric acid has been associated with renal disease, even though hyperuricemia may be a marker of or by itself be responsible for microvascular disease in diabetes (2). In animal models, elevated level of uric acid can lead to arteriolopathy of preglomerular vessels, impaired autoregulation, glomerular hypertension, as well as endothelial dysfunction (3). Kidney damage in hyperuricemic rats is not dependent on blood pressure, and instead involves the renin-angiotensin system. In patients with diabetes, serum uric acid early in the course of diabetes is significantly, and independent of confounders, associated with later development of

persistent macroalbuminuria (4). Therefore, uric acid may be a novel and important player in the pathogenesis of microvascular complications in diabetes. A dose-response relationship between serum uric acid and early decline in renal function has recently been demonstrated in patients with type-1 diabetes (4). In the RENAAL study evaluting type 2 diabetic patients with nephropathy, treatment with losartan lowers serum uric acid levels when compared with placebo treatment (5). This change in serum uric acid was independently associated with a lower risk of doubling of serum creatinine or end-stage renal disease such that approximately one fifth of losartan's renoprotective effect could be attributed to serum ruic acid levels. These data indicate that a reduction in serum uric acid observed during the initial months after starting losartan contributes to its renoprotective effect.

More recently it was shown that higher levels of serum uric acid are independently associated with increased CVD mortality in a type 2 diabetic population (7). Whether increased serum uric acid concentrations are just a risk indicator or a causative risk factor of CVD cannot be determined from epidemiological studies. Higher serum uric acid levels may indirectly contribute to the increased CVD risk through a close association with established risk factors. However, it is conceivable that serum uric acid might confer an excess risk over and above the risk expected as a result of the underlying established risk factors.

Experimental studies in animals have suggested that elevated serum uric acid levels may increase the expression of chemokines and cytokines in the vasculature, activate the reninangiotensin system, and increase systemic C-reactive protein expression (7). Accordingly, treatment with allopurinol may improve endothelial function in hypertensive type 2 diabetic patients with normal serum uric acid levels (8).

Randomized controlled trials on drugs that lower uric acid need to be conducted to evaluate the causal relationship between serum uric acid and development and progression of diabetic cardiovascular and kidney disease.

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The non pharmacological management of hyperuricemia and gout

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Epidemics of gout are historically described in Roman times and in 19th century England; those epidemics were attributed to dietary regimens excessively rich in purines and alcohol, although the widely recognized association with port wine is now thought to be related to lead contamination of fortified wines (1, 2). High plasma uric acid is a prerequisite for gout, which is the most common inflammatory arthritis for adult men. Hyperuricemia is found mainly in postmenopausal women, african americans, patients with renal disease and alcohol abusers (3). Urate is produced mainly in the liver and to a less extent in the small intestine. The production of uric acid mainly depends of purine ingestion but, besides diet, other factors such as obesity, metabolic syndrome, medications (e.g. thiazide and loop diuretics) may be associated with increased plasma concentrations of uric acid, in turn responsible for higher risk of incident gout and higher rate of gout flares. (4, 5). A purine-rich diet would be responsible for an increasing in 1 to 2 mg/dL of uric acid. Therefore, it is recommended that individuals with hyperuricemia should not ingest large amounts of purine-rich food such as veal, bacon, kid meat, mutton, turkey, pork, duck, goose, etc.; evidence exists that high intake of seafood, sugar-sweetened soft drinks, and foods high in fructose may also increase the risk of incident gout; conversely, total protein intake is not related to plasma uric acid. On the other side, dairy intake, folate intake, and coffee consumption are each associated with lower risk of incident gout and lower rate of gout flares. (5). Fructose intake is able to influence plasma levels of uric acid. During fructose metabolism, fructokinase phosphorylates this monosaccharide into fructose 1-phosphate. Next, enzyme aldolase B breaks fructose 1-phosphate into dihydroxyacetone phosphate and D-glyceraldehyde. Following high fructose intake, fructose phosphorylation into fructose 1-phosphate is fast, but the reaction with aldolase is slow. Hence, fructose 1-phosphate accumulates, and inorganic concentrations of intracellular phosphate also decrease. The low availability of

phosphate limits ATP formation with consequent increased catabolism of ADP or AMP, in turn leading to hyperuricemia (6). The intake of sorbitol, sucrose, lactate and methylxanthines may also contribute to increased plasma uric acid concentrations. Sorbitol is converted into fructose by the liver after absorption thus increasing uric acid production (7). In addition to flavonoids, other nutrients contained in fruit and vegetables can increase the plasma total antioxidant capacity. It is likely that the increase of the plasma total antioxidant capacity would be due to the uric acid elevation resulting from fructose metabolism. The cause for such elevation would be the degradation of purine nucleotides or reductions in uric acid excretion (8, 9). In aggregate, vitamin C supplementation significantly lowers serum uric acid but further trials are needed to determine whether vitamin C supplementation can reduce hyperuricemia or prevent incident and recurrent gout (10). High vitamin C intake has a uricosuric effect due to competition of uric acid renal reabsorption through a change in the anion transportation system in the proximal tubule (11). Alcohol intake increases uric acid concentrations and the risk of incident gout by reducing excretion and increasing urate production. Beer intake has a stronger power to increase uric acid than liqueur; this effect is both due to its alcoholic content and high-quality purine; conversely, moderate wine intake does not increase uric acid (12). Dairy product intake has an inverse relation with uric acid concentration because of uricosuric effect probably due to milk-derived proteins (lactalbumin and casein) (12,13). In an experimental model, casein with safflower-seed oil was shown to be effective in attenuating hyperuricemia-associated renal damage, while soy proteins with safflower-seed oil may be beneficial in lowering serum uric acid and triacylglycerol levels (14). The increase of coffee intake decreases uric acid concentrations by improving insulin resistance thanks to chlorogenic acid, an antioxidant contained in the drink (15). Finally, hypocaloric diets indirectly decrease serum uric acid concentrations in overweight individuals by improving insulin sensitivity, regardless of changes in body weight or blood pressure (16, 17). In conclusion the non pharmacological management of hyperuricemia and gout encompasses several therapeutic options, but the role of diet in conditioning serum level of uric acid is supported by robust clinical evidences.

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Gout: Therapeutical aspects in the third millenium

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Gout is due to deposition of monosodium urate (MSU) crystals mainly in and around joints, resulting from long standing elevation of serum uric acid above the saturation point for MSU. The aims of the treatment of gout are not only to treat the acute attaks, but most importantly to obtain the dissolution of the pathogenic crystal deposits and to prevent the excess of cardiovascular deaths.

Acute flares

The most used means to treat acute flares are colchicine and NSAIDs, both of them beeing more active when given early after the onset of flares. Colchicine is a toxic drug when given at high doses, or in the setting of renal or hepatic failure or when coprescribed with macrolide antibiotics, cyclosporin or other drugs which are inhibitors of the P-glycoprotein and/or cytochrome P450. A recent trial has shown that when given early (before 12 hours after flare onset), a small dose of colchicine (1.8 mg) was as effective and much better tolerated than the dose of 4.8 mg traditionally prescribed in the USA. All NSAIDs are active when given at the maximum dose. Smaller dosages are active when given early.

A number of gout patients are unable to tolerate and/or are contra indicated to colchicine and NSAIDs, most commonly because of renal failure, present in roughly 20 p.cent of gouty patients and even more prevalent in severe, advanced gout. Flares can then be treated by steroids and two recent trials have shown that prednisone at the daily dose of 30 mg, given for a week, have equivalent efficacy as a full dosage of NSAIDs. However type 2 diabetes and hypertension are frequently associated with gout and can be contra indications to steroids. Il-1 inhibitors have been shown to be active in these patients and could be used in the near future, but none of them has thus far granted approval for the management of gout.

Urate lowering treatment

Lowering uricemia below the level of MSU saturation allows to dissolve MSU deposits and to cure the disease. This objective, which cannot be reached by the treatments of flares, is of the outmost importance: gout treatment should not focus on flare management only. Urate lowering therapies should target an uricemia below 6 mg/l to allow crystal dissolution and physicians should make sure that this target is reached by measuring uricemia and increasing urate lowering treatment if it is not. Lower uricemias, ie 5 mg/l, should be targeted in severe, tophaceous gout in order to obtain dissolution of the important crystal load in reasonable time. Diet and life style advices are important but are not enough in most cases, leading to the prescription of urate lowering drugs (ULD). Allopurinol is a cheap and very usefull ULD. Recent findings lead to increase very progressively the initial dose of allopurinol as such titration has been shown to decrease the frequency of serious skin reactions. Toxicity, in particular to the skin, may limit the use of allopurinol and renal failure contra indicates increases of the dosage, frequently leading to poor efficacy. Moreover, allopurinol when given at the usual dosage of 300 mg/d presently allows to reach the target uricemia of 6 mg/l in only a minority of gouty patients, in contrast with what was observed in the seventies when this dosage was regularly efficient. Febuxostat is a more potent xanthine oxydase inhibitor. 80 or 120 mg/d of febuxostat have been shown to be more efficient that allopurinol 300 mg/d. Moreover the precription of febuxostat is not modified by creatinine clearance decrease down to 30ml/min, which is a valuable advantage in CKD patients. Pegloticase is a pegylated uricase, administered bimonthly by the IV route, which has been recently approved in the USA for severe refractory gout. This potent and expensive drug allows dramatic reduction of uricemia and rapid disapearance of tophi. Unfortunately high antibody titers develop in 40 p. cent of patients leading to reduced efficacy and infusion reactions. A number of ULD are Under development including uricosurics. Lesinurad, an inhibitor of URAT1 renal transporter is entering phase 3 trials and may become available in the near future. Most probably the drug will be added to allopurinol when allopurinol alone fails to reach the uricemia target.

The main problem of ULDs remains the poor adherence of patients to these drugs. It has been estimated that only 50 p.cent of patients prescribed allopurinol remain on the drug after one year, whereas the treatment whould be given life long. Patient education is therefore of the outmost importance when prescribing a ULD. One particularity of gout among the chronic diseases, is that ULDs initialy cause dispersion of the crystal deposits and frequently trigger flares during the first months of treatment leading patients to discontinuate these drugs. Patients shoud therefore be informed of this transient side effect (which stop when crystals are fully dissolved) and prophylaixs should be precribed. Small dose colchicine or NSAIds for 6 months or more, indeed allow efficient prevention of the triggered flares. In patients who cannot take colchicine or NSAIDs, IL1 inhibitors are efficient, although not yet approved.

Treatment of comorbidities

Componets of the metabolic syndrome are frequently associated with gout and should be diagnosed ant treated to reduce cardiovascular risk. Among these obesity should be treated. Loss of weight not only improves the cardiovascular outcome but also lowers uricemia. Management of hypertension should be obtained without diuretics as diuretics increase uricemia. Losartan and calcium inhibitors should be favored as they decrease uricemia. Type 2 diabetes should also be treated. All measures which decrease insulinemia, such as weight loss, biguanides or glitazones decrease uricemia.; Treatment of hyperlipemia by fenofibrate or artovastatine has also been shown to decrease uricemia. All CV risk factors, including smoking, should be adressed.

The Challenge of Gout Management in the Elderly

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Elderly people are now the most rapidly growing proportion of the patient population in the majority of Western countries, and aging seldom comes alone, often being accompanied by chronic diseases, comorbidity, disability, frailty, and social isolation. Gout represents one the most relevant clinical condition of the aging population. The prevalence of gout increases dramatically with age, with almost 12% of males aged 70–79 years affected compared with <3% in men younger than 50 years (1,2).
Elderly gout includes elderly onset gout and subjects with chronic persistent gout that started before age 65. Elderly gout differs from classical gout found in middle-aged men mainly due to polyarticular presentation with upper-extremity-joint involvement, fewer acute gouty episodes, indolent clinical course and an increased incidence of tophi especially of the elbows and hands (3). From an epidemiologic standpoint, gout in the elderly tends to have a more equal gender distribution and there is a stronger association with comorbidities including hypertension, metabolic syndrome, diabetese, acute myocardial infarction and stroke (4-8). A positive association between high circulating levels of uric acid and dementia syndrome has been also recently described which, at least in part, is independent of most cardiovascular, cerebrovascular and metabolic risk factors (9). Gouty arthritis, when not adequately attended to, can be a functionally disabling disease that can lead to a substantial decrease in quality of life in the elderly population. The diagnosis of gout can be more challenging in the elderly than in younger persons due to mimicking other arthritis including septic and rheumatoid arthritis. In addition, gout can be mistaken for changes that are usually attributed to osteoarthritis. Indeed, tophi can supervene on Heberden's and Bouchard's nodes (10). Some of the distinguishing features of gouty arthritis are the asymmetrical distribution of the tophaceous joint swelling, and the presence of typical radiographic findings of

tophaceous gout. The gold standard in establishing the diagnosis is the demonstration of the presence of monosodium urate crystals, typified as negatively birefringent needle-shaped crystals on light and polarizing microscopy of synovial fluid (11).

The effective management of gout in the elderly is challenging as global clinical condition of people in this demographic segment can be frequently complicated by substantial comorbidities: up to 58% of patients with gout have comorbid hypertension, 45% have a comorbid lipid disorder, 33% have both hypertension and a lipid disorder and 20% have comorbid diabetes mellitus (12). Multiple diseases and multimorbidity inevitably lead to the use of multiple drugs, a condition known as polypharmacy. Over the last 20-30 years, problems related to aging, multimorbidity, and polypharmacy have become a prominent issue in global healthcare. Although the guidelines of gout treatment are the same in the elderly as in the general population, recognition of the physiological changes that affect medication metabolism, drug interactions, and medical comorbities in older individuals is paramount (12). For the acute treatment of gout, the benefits must be weighed against the risks, especially in the elderly. One must consider that an acute gout flare is self-limited, and that the acute flare should resolve on its own without intervention. Given the higher rates of chronic renal insufficiency, polypharmacy, and other comorbid conditions, the use of medications for acute gout must be individually tailored to each elderly patient (13). Although colchicine has been used to treat acute gout for decades, caution should be used when prescribing this medication in the elderly due to its side-effects profile including severe gastrointestinale manifestations, which can include nausea, vomiting, diarrhea, and abdominal pain (12). The toxic effects of colchicine are potentiated in patients with renal and hepatic insufficiency. Recently published consensus guidelines for the dosing of several renally cleared medications in older patients indicates that colchicine is recommended not to be used in patients with a creatinine clearance of less than 10 mL/min/1.73m^2 (14). For the management of an acute gout flare, the use of nonsteroidal anti-inflammatory drugs is an effective option for treatment (12). However, chronic use of these drugs is not recommended in the elderly due to the increased risk of

upper gastrointestinal bleeding and the concern of concurrent renal insufficiency which could be worsened by nonsteroidal anti-inflammatory drugs use (15).

The decision to initiate uric acid–lowering therapy depends on the presence of subcutaneous tophi or an unacceptably high rate of gout flares. Furthermore, the growing body of evidence indicating an unfavorable impact of increased serum uric levels on cardiovascular and renal diseases suggests the opportunity to pay attention to uric acid levels independently on the diagnosis of gout in the elderly. The target serum urate level should be lower than 6.0 mg/dL as the solubility of uric acid has been demonstrated to be at 6.8 mg/dL (12). It is critical that this level is achieved, as crystal deposition can occur at any concentration above this. Allopurinol is the most frequently prescribed medication for lowering uric acid (12,16). Once daily dosing, as well as the demonstrated efficacy in lowering uric acid, make it an attractive therapy (12). Allopurinol is metabolized in the liver to its active metabolite, oxypurinol which is secreted primarily through the kidneys, with a half-life of approximately 16 to 18 hours. In the growing geriatric population, the prevalence of declining renal function and the risk of polypharmacy have to be taken in account by clinicians when prescribing allopurinol (17). In addition, adjusting allopurinol doses based on creatinine clearance may not be sufficient to achieve a goal serum urate level of less than 6.0 mg/dL (18). The new xanthine oxidase inhibitor febuxostat has been demonstrated to be effective and safe in lowering uric acid levels (19). Although the metabolites of febuxostat are generally higher in patients with renal impairment, an 80-mg once-daily dose seems to be well tolerated in patients of differing renal function (20). Thus, there are no dosage adjustments that are recommended in patients with mild-to-moderate renal insufficiency (20). In addition, the pharmacokinetics and pharmacodynamics of febuxostat in elderly subjects is similar to that observed in younger subjest (21). Phase III trials that have documented the efficacy of febuxostat when compared with allopurinol. The Febuxostat versus Allopurinol Control Trial (FACT) compared patients who received febuxostat (80 mg or 120 mg) with patients who received allopurinol 300 mg (22). At the end the study the use of febuxostat at either 80 mg or 120 mg doses was more

effective than allopurinol 300 mg in lowering serum urate levels (22). In addition, data obtained from the 374 elderly subjects enrolled in CONFIRMS study demonstrated that febuxostat 80 mg and 40 mg is superior to commonly prescribed fixed doses of allopurinol (200/300 mg) in subjects ≥65 years of age with high rates of renal dysfunction and is well tollerated (23). Thus, for the elderly patients febuxostat would represent a good treatment choice.

In conclusion, there are differences in the clinical features and approaches to the treatment of gout in the elderly as compared with the general population. As the presentation of gout in the elderly is more indolent, particular attention has to be posed a polyarticular, progressive arthritis which represent a relevant index of suspicion for gout in the elderly patients. From the treatment standpoint, although the same pharmacologic agents are used in the elderly, great caution is required when these drugs are used in the elderly as there are many comorbidities that can affect medication management.

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Uric Acid and Antihypertensive Therapy

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The concept that uric acid and arterial hypertension are intimately ligated is an old one, prospective initial descriptions of the relationship between uric acid and arterial hypertension in the 1960s described that twenty-six percent of untreated hypertensive patients with normal renal function had elevated serum uric acid concentrations. This figure rose to 58% among those receiving antihypertensive therapy, particularly in those receiving diuretics (1). The presence of elevated uric acid levels in normotensive, borderline and established hypertensives was shown to be associated with decreased renal blood flow without affecting glomerular filtration rate and with increased renal and peripheral resistances suggesting that unexplained hyperuricemia in patients with essential hypertension most likely reflects early renal vascular involvement, specifically, nephrosclerosis (2). On the other hand, it is also known that hypertension is one of the most common comorbidities of gout and that the presence of hypertension is independently associated with incident gout (3).

In recent times there has been a rekindled interest in the role of uric acid in cardiorenal disease. Epidemiologic analysis consistently find that uric acid level predicts the development of chronic kidney disease (4), while recent meta-analysis find that uric acid predicts the development of hypertension (5), diabetes (6) and stroke (7). The relationship between coronary artery disease and uric acid remains still controversial.

In this issue of the Journal Choi et al (8), describe an interesting case-control study nested within a UK general practice database where they examined the independent associations of antihypertensive drugs with the development of incident gout, stratified by the presence of hypertension. They found that compatible with their urate lowering properties facilitated through an increased uricosuria, calcium channel

blockers and losartan are associated with a diminished risk of incident gout when used to treat hypertensive patients. The multivariate relative risks were respectively 0.87 and 0.81 for calcium channel blockers and for losartan. These figures compared with a risk of 2.36 for diuretics, 1.48 for beta-blockers, 1.24 for angiotensin-converting enzyme inhibitors and of 1.29 for the rest of angiotensin receptor blockers. Interestingly, similar results were found in the normotensive group.

The interest of these findings radicate in the opinion of the authors in the fact that the use of urate lowering antihypertensive drugs could help to diminish the high comorbidity burden of gout and hypertension in patients at high risk of developing gout (3). To this it can be added that the diminution in serum uric acid levels obtained with losartan in comparison with atenolol in the LIFE trial appeared to explain 29% of the treatment effect on the primary composite end-point consisting of fatal and non-fatal myocardial infarction and stroke (9). Similarly the decrease in uric acid observed with losartan in comparison with placebo in the RENAAL study was associated with the degree of long-term renal risk reduction which explains a part of the renoprotective effects of losartan (10). The possibility that allopurinol can be effective for renal and cardiovascular protection in hyperuricemic subjects has been recently proponed (11). Evenmore, in young hyperuricemic hypertensives the administration of allopurinol has been shown to be followed by a significant fall in blood pressure.

In summary, hypertension and hyperuricemia frequently coexist. Antihypertensive therapies exert different effects on the development of incident gout in hypertensive patients with losartan and calcium channel blockers presenting the lowest hazard ratios, due to the uricosuric properties of these drugs. A descent in the level of serum uric acid could beyond diminishing incident gout improve the cardiovascular and renal outcome of these patients.

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Serum uric acid levels, gout and progression of renal disease

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Epidemiological studies have long yielded contrasting results on the independent role of uric acid in predicting the development of kidney disease ([1], [2]). This has been taken to suggest that mild increases in uric acid may be a marker of diminished kidney function rather than a direct cause of kidney disease. Nevertheless, strong evidence favouring a role for uric acid in the development of kidney disease has recently been published ([3]).
Serum uric acid may induce kidney damage both directly and indirectly by promoting several well known mechanisms of renal damage. To date, only a few, underpowered studies have investigated the effect of pharmacological reduction of SUA. Following serum urate lowering treatment, there have been reports of improvement in blood pressure control and delay in the progression of kidney damage ([4], [5]). The impact of allopurinol on the risk of mortality was analyzed in a large sample of elderly hyperuricaemic patients ([6]). In the incident allopurinol users, this treatment was associated with an almost 25% lower risk of all-cause mortality as compared to non users. Randomized studies have shown improvements in blood-pressure control (17), CV damage ([7]) and slowing of CKD progression ([8]) following pharmacologic urate lowering. However, most studies were short-term, small sized, and often single-centre. A newer, selective xanthine-oxidase inhibitor (i.e. Febuxostat) which may have several potential advantage over allopurinol, has recently became available. Long term clinical studies on hard renal end point with this drug are very much needed. Currently, it remains unclear whether the benefits observed by urate-lowering treatment are due to favourable effects of the drug itself or are mediated by its action on XO activity ([9]). Further studies are needed to confirm the possible role of SUA as a surrogate end point of treatment.

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Gout and cardiovascular diseases: what is the evidence?

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Since the old definition of *Gutta Visceralis* the acute arthritis induced by needle-like crystals of uric acid precipitating in joints was suspected to be responsible for other pathologic conditions.
At the present time, gout and hyperuricemia are supposed to act as risk factors for cardiovascular disease – including stroke and peripheral artery disease – and renal insufficiency. Further, they are also under investigation as contributors to the development of the metabolic syndrome. Finally, hyperuricemia is a very common component of the metabolic syndrome, even if its presence is not necessary for the definition.
Many studies have frequently failed to distinguish whether hyperuricemia has an independent effect on cardiovascular risk or serve as markers for other risk factors. However, interesting findings recently derived in this field by post hoc analyses of datasets from the Aspirin Myocardial Infarction Study (AMIS), a 1:1 randomized, double-blind clinical trial, that examined mortality rates following daily aspirin administration over three years in individuals with documented MI. The primary outcome measures were all-cause death, coronary heart disease (CHD) mortality, coronary incidence, and stroke by quartile of baseline serum uric acid. Of 4,524 enrolled participants, data on 4,352 were analysed. All outcomes were greatest for patients in the fourth quartile of serum uric acid. In multivariate regression models, the hazard ratios for patients in the highest quartile were 1.88 for all-cause mortality (95% confidence interval (CI), 1.45 to 2.46), 1.99 for CHD mortality (95% CI, 1.49 to 2.66), and 1.36 for coronary incidence (95% CI, 1.08 to 1.70). Of note, patients with untreated gout had an adjusted hazard ratio ranging from 1.5 to 2.0 (all $P < 0.01$) for these outcomes while those with gout who were receiving treatment did not exhibit this additional risk.
In keeping to these clinical findings, *in vitro* uric acid has potentially protective effects as a strong antioxidant, approaching the potency of

vitamin C. However, *in vivo* uric acid seems to act as a pro-oxidant and pro-inflammatory agent. Thus, it is easy to understand the reasons leading to the progressive elevation of serum uric acid levels that we have recently observed in both female and male patients with the metabolic syndrome, based on the number of metabolic syndrome components. Of particular interest, while we found serum uric acid concentrations were significantly related to the degree of insulin resistance in patients with the metabolic syndrome but not in control subjects, experimental studies have strongly suggested that uric acid is a biologically active compound that can increase inflammatory mediators – such as interleukin 1β, NF*K*B, and others – known to lead to vascular damage. Concordant to this, drug-induced reduction of serum uric acid levels was accompanied – at least in markedly hyperuricemic patients (> 9.5 mg/dL) – by clinical improvements in patients with heart failure, and reduction of blood pressure in hyperuricemic adolescents.

Considering the above findings, more clinical trials are needed to elucidate this topic, particularly by the use of older drugs – as allopurinol and oxypurinol – in comparison to newer and more potent ones, as febuxostat. Meanwhile, evidence seems to strongly support the needing to consider hyperuricemia (≥ 6 mg/dL and even lower in female patients) and urate crystal deposition as a target in cardiovascular, renal, and metabolic protection.

Serum uric acid and CV risk: a look into epidemiology

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Cardiovascular diseases are the major cause of death in the Western world as a consequence of the elevated prevalence and poor control of cardiovascular risk factors in the general population. During the last 25 year many possible risk modifiable factors have been identified in addition to those included in the main CV risk algorhytms as elevated blood pressure, diabetes and lipid disorders. Elevated levels of serum uric acid are the mechanism responsible for the development of gout but have been also frequently associated with an increase in the individual risk of CV diseases in addition with the more consolidated CV risk factors. A recognition of an association among hyperuricemia, kidney diseases and cardiovascular diseases dates to the late 19th century, but has been recently resurged to investigation in reason of the increase in the amount of information about the possible pathogenetic mechanism(s) and the demonstration of a remarkable degree of residual cardiovascular risk in patients undergoing an approriate control of the many independent CV risk factors. The hypothesis linking uric acid with cardiovascular disease is well grounded in animal models where the development in hyperuricemia is associated with an increase in blood pressure that can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in serum uric acid. Data from observational studies and physiological experiments suggest that there may be a causal relationship between plasma levels of uric acid and the incidence of cardiovascular and renal disease. However, definetely convincing evidence remains elusive for many different reasons that complicates the relationship between the study of uric acid, its determinants and its confounders. In particular among the confounders a prominent role is played by statistical and methodological issues as well as by the counfonding role of co-variates that might be also mediators of biological pathways (e.g kidney) or might variably interact with additional cardiovascular risk factors. In particular the assessment of the role of uric acid as a risk factor for CV diesase should be conducted in patients free from

gout and kidnery disease, with a balanced age-range and gender distribution and across a appropriate period of follow-up. Cross-sectional investigations that have been often claimed to confirm or deny the association between uric acid and CV disease are difficult to interpret because of the elevated number of co-morbidities that affect the subjects. However despite these limitations in the methodological approach, the possible association between s.uric acid and cardiovascular disease is well supported by several epidemiological observation, can be reasonably explaind by a mechanicistc approach and might be favorably modified by appropriate treatment strategies involving both a biochemical and a structural approach addressing the protection of target organ. Understanding the complex relationship between uric acid and cardiovascular diseases is necessary to quantify of uric acid as a risk factor and should force the researches and clinicians to balance evidence supporting causality vs. associations. From the epidemiological point of view the association between uric acid and subsequent cardiovascular disease remains uncertain. While some recent recent epidemiological studies have independently related uric acid to hypertension, diabetes, metabolic syndrome, renal disease and cardiovascular complications, other studies have found that, following adjustements for cardiovascular risk factors and estimated GFR the independent role of uric acid in cardiovascular disease cannot be confirmed.

All these evidence support a possible role of serum urinc 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.

Uric acid and the endothelium

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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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Uric Acid and Cerebrovascular Diseases

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Uric acid (UA) is the end product of purine catabolism in humans. It is produced through a reaction mediated by xanthine oxidase in which high amounts of hydrogen peroxide - a prooxidant molecule- are concomitantly generated. In spite of being the major endogenous antioxidant in blood,[1] high levels of UA have been linked to higher risk of cerebrovascular disease.[2] However, as it will be discussed, the causal relationship between hyperuricemia and the risk of cerebrovascular disease is controversial. It remains to be clarified whether hyperuricemia represents a risk factor on its own or otherwise an innocent bystander in individuals with other well-established cardiovascular risk factors. Ongoing trials involving urate lowering therapies will add robust evidence on the link between UA and cardio- and cerebrovascular disease.

Otherwise, oxidative stress is one of the main mechanisms implicated in the physiopathology of acute ischemic stroke, and the use of antioxidant molecules, such us UA, has shown robust neuroprotective properties in experimental ischemia, as it will be reviewed.[3] In rats, the exogenous administration of UA is neuroprotective and the benefit is additive to the protection provided by the thrombolytic agent alteplase.[4] In patients suffering an acute ischemic stroke, higher UA levels at stroke admission are associated with better outcome and less infarction growth at follow-up and there exists a rapid consumption of UA after stroke.[3,5] In a recent Phase II, the combination of UA administered intravenously and the thrombolytic agent alteplase was safe and prevented an early fall of circulating UA levels.[5] As a measurable biological effect, UA also prevented an increment of a marker of malondialdehyde -a lipid peroxidation marker- and of active MMP9 -a marker of blood brain barrier integrity. [6] According with these evidences, an ongoing Phase III trial -the URICOICTUS trial- is

currently testing the clinical efficacy of UA administration in acute ischemic stroke patients.[7]

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Uric acid and clinical prognosis in patients with pre-eclampsia

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Pre-eclampsia is a clinical syndrome defined as the new onset of hypertension and proteinuria during the second half of pregnancy. It affects approximately 2-8% of all pregnancies and is associated with several complications. Pre-eclampsia is a leading cause of maternal mortality, especially in developing countries. In developed countries, pre-eclampsia is an important cause of premature delivery because the only known remedy is delivery of the placenta.

The diagnosis of pre-eclampsia is clinical requiring blood pressure ≥ 140/90 mmHg on two occasions combined with urinary protein excretion > 300 mg/d. Edema, once a classic feature of the disease, is no longer considered a diagnostic feature given its lack of sensitivity and specificity. Laboratory tests such as liver function tests, quantification of urinary protein, and serum creatinine may be helpful in characterizing the degree of end-organ damage but none is specific for pre-eclampsia.

Hyperuricemia, which is more likely to be present in women with pre-eclampsia than in normotensive pregnant women, has been used as a diagnostic aid and to predict adverse outcomes in pre-eclampsia, but its predictive value is generally modest.

In normal pregnancy, serum uric acid concentrations decrease as a result of pregnancy-induced expansion of the volume, increase in renal blood flow and glomerular filtration rate, and the uricosuric action of estrogen. By mid-pregnancy, serum uric acid concentrations usually are in the 3-4 mg/dl range (180-240 μmol/l). They then slowly increase reaching 4-5 mg/dl (240-300 μmol/l) by term.

In patients with pre-eclampsia, serum uric acid concentrations are relatively increased compared with normal pregnancy. The primary

mechanism for the increased serum uric acid in pre-eclampsia is a reduction in renal excretion of urate, which is probably mediated by the system vasoconstriction, reduction in renal blood flow and decrease in glomerular filtration rate that accompany this disease. There is also evidence for increased generation of uric acid from the ischemic placenta.

There are a number of epidemiological features that link uric acid to pre-eclampsia.

1. Individuals at risk for developing pre-eclampsia often have high serum uric acid before pregnancy (e.g., obesity, black race, insulin resistance, and essential hypertension are predisposing factors for the development of pre-eclampsia).
2. In patients destined to develop pre-eclampsia, one of the earliest biochemical changes is a decrease in renal urate excretion, which can be detected as early as the first trimester (13 weeks). Serum uric acid subsequently increases; by 20-28 weeks, there is a tendency for greater uric acid concentrations in individuals who will develop pre-eclampsia than those who will not. However, because of overlapping values, uric acid concentrations were found to be minimally predictive of the development of pre-eclampsia in one study, and not predictive in the others.
3. Serum uric acid is increased in the individual once pre-eclampsia has developed. The degree of the increase has been correlated with the severity of the maternal syndrome including the renal biopsy findings. Uric acid concentrations are the greatest in those with eclampsia, followed by pre-eclampsia, pre-eclampsia complicating pre-existing hypertension, gestational hypertension, and normal pregnancy. However, because of the significant overlap in uric acid values among the hypertensive groups, uric acid was not clinically useful in distinguishing pre-eclampsia from gestational hypertension.
4. A number of studies have also reported that serum uric acid can predict fetal outcome in individuals with pre-eclampsia. Several groups have reported that the ability of uric acid to predict fetal outcome is best when it is measured before 35 weeks, although most studies still show a significant inverse relationship between

uric acid and birth weight in pre-eclamptic individuals at the time of delivery.

5. Serum uric acid is intricately linked to the pre-eclamptic syndrome. Although serum uric acid may be clinically useful as a predictor for the development of pre-eclampsia, it is generally increased in these women once they manifest the disease, and the degree of increase thus correlates with maternal and fetal risk, particularly when measured early in the course of severe disease. These studies thereby raise the possibility that increased uric acid concentrations might contribute to the pathogenesis of the clinical syndrome.

There has been only one study in which allopurinol was randomly administered to individuals with pre-eclampsia. Allopurinol (200 mg) with vitamins E and C or placebo were given to patients with established pre-eclampsia beginning 25 weeks of pregnancy. The allopurinol group had a longer period before delivery but there were no differences in maternal complications and fetal outcome. However, in this study, uric acid concentrations during allopurinol treatment were still greater than 5 mg/dl. The study does not adequately address the issue whether decreasing uric acid concentrations to values associated with normal pregnancy can prevent or treat the pre-eclamptic condition.

A study from Magee-Womens Research Institute in Pittsburgh, USA, found uric acid as important as proteinuria in identifying fetal risk in women with gestational hypertension. Similar results were obtained by a retrospective cohort study by Hawkins et al. showing that hyperuricemia in hypertensive pregnancy remains identifies women at increased risk of adverse maternal, and particularly fetal outcome; the latter even in women with gestational hypertension and without any feature of pre-eclampsia.

In conclusion, serum uric acid is increased in women with clinically evident pre-eclampsia. However, there is no consensus as to the sensitivity and specificity of hyperuricemia as a prognostic indicator of future pre-eclampsia. On the other hand, there is growing evidence

that hyperuricemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and fetal outcome. A worsening of serum uric acid in women with pre-eclampsia and/or HELLP (hemolysis, elevated liver enzymes, and low platelets) is a useful indicator when considering elective delivery.

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Uric Acid in Overweight and Obese Patients

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Animal studies have shown that in different experimental models of obesity, metabolic syndrome and diabetes uric acid may exert a number of unfavorable effects on adipose tissue, favoring the development and progression of pro-inflammatory endocrine imbalance of the adipocites.

Elevated blood levels of uric acid have been frequently reported in patients with obesity and metabolic syndrome. In this latter condition uric acid levels are directly related to the different components of metabolic syndrome, and in particular with central adipose tissue depot. In addition, recent studies have shown that elevated serum uric acid levels are indipendent predictors of visceral obesity, hyperinsulinemia and other metabolic abnormalities commonly detectable in the obese state.

This presentation will be focused on the relationships between uric acid, overweight and obesity, including epidemiological data collected in a number of studies. Special focus will be made on the analysis of the relationships between uric acid and normal or abnormal body weight and body mass index found in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA). Recent analysis of the PAMELA data has allowed to provide new information in the general population on the relationships between uric acid and 1) clinic, home and ambulatory blood pressure values, 2) target organ damage and 3) cardiovascular events.

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