Review

Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout

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Abstract

For many years, the relationship between cardiovascular disease risk and gout, though strong and consistent, was suspected of being coincidental rather than causative. In recent years, compelling epidemiological and clinical data have increasingly favoured an aetiological connection. However, that connection is notably complex, involving a multifaceted model that includes interactions between inflammatory processes, oxidative stress and potential genetic influences, as well as cardiovascular and renal components that remain only partly explained. Urate appears to be able to activate the immune response, and in that context has a mediating role in the inflammatory process via the inflammasome. This interaction of urate and inflammation is central to the inflammatory cascade associated with gout flares. In the arena of oxidative stress, urate has both antioxidant and pro-oxidant properties, and while potentially beneficial in scavenging free radicals, it can also impair endothelial function and thereby give rise to atherosclerotic risk. Human and animal studies have revealed associations between hyperuricaemia and a host of atherosclerotic risk factors, whereas a reduction in urate levels is frequently associated with improvement or even resolution of such risk factors. The degree to which reduction of serum urate can reliably improve cardiovascular risk remains uncertain. It is hoped that the introduction of newer urate-lowering agents may help to clarify this picture and improve treatment options for both gout and atherosclerosis.

Key words: Atherosclerosis, Cardiovascular disease, Gout, Hyperuricaemia, Inflammasome, Inflammation, Oxidative stress, Urate.

Introduction

The prelude to a scientific understanding of the nature of gout can be traced as far back as 1679 when Van Leeuwenhoek made drawings of gouty tophi based upon his microscopy studies, although at the time he had no knowledge of the composition of the crystal depositions he observed [1]. It was more than a century before Wollaston [2] identified the crystalline material of tophi as being sodium urate, the discovery of which was first published in 1797. Another half century passed before Alfred Garrod was able to establish that an elevation of uric acid in the serum is a hallmark of gout [3]. In a subsequent landmark study, published in 1854, Garrod described his ‘Uric Acid Thread Experiment’, in which he isolated uric acid crystals from the serum of a gout sufferer [4]. In the ensuing century and a half, much has been learned about gout and its associations with other pathologies, but as more data are gathered, the complexity of gout and its relationship to inflammation, atherosclerosis, oxidative stress and a variety of other interlinked functions and dysfunctions has made a unified theory of gout seem both nearer and ever more elusive.

As Wollaston and Garrod made clear, people with gout have elevated levels of urate. And yet, possession of elevated urate does not imply gout, since only a relatively small proportion of people with hyperuricaemia actually suffer from the condition [5–7]. The National Health and Nutrition Examination Survey III (NHANES III) found that between 1988 and 1994, 5.1 million adults (>20 years) reported receiving a physician’s diagnosis for gout, representing 2.7% of the adult population [8]. An increased incidence of gout in both men and women was associated with advancing age. Since the NHANES III study was completed, there has been strong evidence that the incidence and prevalence of gout is increasing at a rapid
rate. An analysis of a large managed care database observed a prevalence rate of 2.9% per 1000 people in 1990 [9]. By 1999, the prevalence had increased to 5.2 per 1000 people.

Comorbidities in gout and hyperuricaemia

Awareness of an association between gout and a variety of diseases and pathologies has existed since antiquity, but the anecdotal has in more recent years been solidified by a gathering mass of epidemiological and clinical data confirming the involvement, or at minimum the concur-
rence, of gout with a host of comorbidities. Such comor-
bidities are made up to a large degree by risk factors for cardiovascular disease (CVD). A 2-year retrospective analysis of claims from managed care enrollees across the USA found that among 9482 gout and hyperuricaemia patients, the most common comorbidities were hypertension (57.9%), lipid disorders (45.3%), respiratory and chest symptoms (35.3%) and diabetes mellitus (19.9%) [10]. These rates for hypertension and diabetes are approximately double those of the general population, whereas the rate of dyslipidaemia seen in these gout and hyperuricaemia patients is approximately triple that of the population at large [11]. Also of note is the fact that coronary atherosclerosis was seen in 15.5% of the gout and hyperuricaemia subjects and cardiac arrhythmias in 10.5%.

A study of patient records from general practitioners in the UK (2.5 million patients) and Germany (2.4 million patients) identified 34 797 subjects with gout and found similar comorbid patterns [12]. The most common comorbidities were obesity, CVD, diabetes and hypertension. A correlation was also observed between increasing levels of serum uric acid (sUA) and increasing risk of comorbid-
ities [12]. Twelve-year data from the Health Professionals Follow-Up Study—a long-term longitudinal questionnaire-based study of male health care professionals—found that among the more than 47 000 subjects being prospectively tracked, 730 confirmed cases of gout were identified [13]. Among these, the researchers found that the presence of hypertension was associated with a relative risk (RR) for gout of 2.31 (95% CI 1.96, 2.72) [13]. A BMI of 30–34.9 was correlated with an RR of 3.26 (95% CI 2.28, 4.65), whereas a BMI ≥ 35 conferred an RR of 4.41 (95% CI 2.59, 7.51) [13]. Weight gain was additionally associated with an elevated risk of gout, whereas weight loss resulted in a reduced risk of gout [13].

Gout and hyperuricaemia as CVD risk factors

The association between both hyperuricaemia and gout with risk factors for CVD is strong and consistent (Table 1). An analysis of data from the Framingham Study, with a follow-up of 32 years, found that men with gout were 60% more likely to experience coronary heart disease (CHD) than those without gout (95% CI 1.1, 2.2) [14]. It should be noted that this was largely a result of a doubled risk for angina pectoris. Data from the Multiple Risk Factor Intervention Trial (MRFIT) showed that among 9105 men (age range 41–63 years) who possessed an elevated risk for CHD, the hazard ratio (HR) for CHD-related mortality was 1.35 among those with gout compared with those without (95% CI 1.06, 1.72; P = 0.01) [15]. The HR for death from acute myocardial infarction (MI) was also 1.35 (95% CI 0.94, 1.93; P = 0.09) for gout vs no gout, whereas death from CVD in general was 1.21 for men with gout (95% CI 0.99, 1.49; P = 0.06). Interestingly, an

### Table 1 Cardiovascular disease-related morbidity and mortality in gout vs non-gout patients

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>n (with gout)</th>
<th>Mean follow-up, years</th>
<th>Risk factor</th>
<th>Increased risk in gout patients</th>
<th>Statistical significance, 95% CI; P-value</th>
<th>Comment</th>
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<td>Framingham [14]</td>
<td>686</td>
<td>7.3 (2-year risk)</td>
<td>CHD</td>
<td>RR 1.6</td>
<td>1.1, 2.2</td>
<td>Data refer only to male patients; increased risk was primarily due to elevated rates of angina pectoris</td>
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<td>MRFIT [15]</td>
<td>9105</td>
<td>6.8</td>
<td>CHD-related mortality</td>
<td>HR 1.21</td>
<td>0.99, 1.49; 0.06</td>
<td>Patient population was all male, with an elevated CHD risk</td>
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<td>MRFIT [16]</td>
<td>1123</td>
<td>6.5</td>
<td>Acute MI</td>
<td>HR 1.35</td>
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<td>Health Professionals</td>
<td>2773</td>
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<td>CVD-related mortality</td>
<td>OR 1.26</td>
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<td>Follow-up Study [17]</td>
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<td>CHD-related mortality</td>
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<td>Non-fatal MI</td>
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analysis of mortality risk in MRFIT for men with hyperuricaemia but not gout showed no significant correlation with CHD-related mortality (HR = 1.09), death from acute MI (HR = 1.04) or overall CVD mortality (HR = 1.11) [15].

These data may be compared with an earlier analysis specific to acute MI in nearly 13,000 subjects from MRFIT who had been followed for a mean of 6.5 years. In that study, the odds ratio (OR) for experiencing acute MI was 1.26 (95% CI 1.14, 1.40) and 1.11 (95% CI 1.08, 1.15; P < 0.001) for men with gout and hyperuricaemia (with or without gout) [16]. Subgroup analyses of these data further determined that a statistically significant association persisted between acute MI and both gout and hyperuricaemia even after potentially confounding factors, such as aspirin use, alcohol use, presence of metabolic syndrome, were accounted for. Taken together, these data point to the possibility that something in the nature of gout, as opposed to hyperuricaemia per se, exerts an increased risk of mortality from CVD.

Additional prospective data from more than 51,000 men in the Health Professionals Follow-Up Study confirms the mortality data reported in MRFIT. Over a period of 12 years, the RR for CVD-related death was 1.38 for men with gout (95% CI 1.15, 1.66) and 1.55 for CHD-related mortality (95% CI 1.24, 1.93) [17]. In addition, the RR for non-fatal MI in men with gout was 1.59 (95% CI 1.04, 2.41) [17].

Recently reported data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, in which nearly 3000 younger men and women (mean age 40 years) without baseline CVD were followed for 15 years, found that increased sUA conferred a significant risk for subclinical atherosclerosis as determined by the presence of coronary artery calcification [18]. This effect was seen even after controlling for confounding factors, such as metabolic syndrome, diabetes, hypertension and hyperlipidaemia. Similar results have been seen in other recent studies [19]. In the National Heart, Lung and Blood Institute Family Heart Study, 4866 men and women were measured for both sUA and carotid atherosclerotic plaques, the latter indicating preclinical CVD. An association between elevated sUA and the presence of carotid atherosclerotic plaques was observed in men but not in women after controlling for confounding factors [20]. Thus, it would appear that hyperuricaemia may not be benign even when asymptomatic.

Based on these data, it is reasonable to conclude that an independent association for both gout and hyperuricaemia with respect to CVD has been established. That said, association does not prove causation. Indeed, elevated levels of urate are frequently observed among patient populations already at a heightened risk for CVD. Having metabolic syndrome, for example, confers a strong probability of being hyperuricaemic. Data from NHANES III showed that individuals with uric acid levels of <6 mg/dl had a prevalence rate of 18.9% for metabolic syndrome, rising to 36.0% at 6–6.9 mg/dl, 40.8% at 7–7.9 mg/dl and 59.7% at 8–8.9 mg/dl [21]. Both hypertension and renal disease have also been strongly associated with hyperuricaemia, whereas other factors, including ethnicity—such as being African-American—or being menopausal are additional risk factors for hyperuricaemia [22–24].

A 2008 study by Choi et al. [25] found that intake of fructose in soft drinks was associated with an increased risk of gout, and that the risk increased as the intake of fructose-sweetened drinks increased. Although it has long been known that hyperuricaemia can be induced by fructose consumption [26], possibly by the resultant hyperinsulinaemia [27], this is the first time fructose has been directly associated with gout risk. It is also consistent with data showing increased metabolic syndrome, glomerular hypertension and renal microvascular damage in rats that have been fed fructose [28]. Future mechanistic research will be able to decide if this association is merely a manifestation of confounding by fructose-induced hyperinsulinaemia.

Although a link between CVD and gout has long been understood to exist, research as to the specific nature of this association was neglected to a large degree until relatively recently. This was due in part to the fact that many researchers felt the link between gout and CVD to be confounding rather than causative, and to date, the latter remains unproved if strongly suspected. Nevertheless, while a preponderance of data point to a pathophysiological link, some data do exist that contradict this notion. For example, a Dutch case-control study of approximately 12,000 primary care patients, which included 261 with gout, observed no evidence that gout was an independent risk factor for CVD [29]. It should be noted, however, that this study’s reliance on the International Classification of Health Problems in Primary Care coding system for identifying study subjects may limit the reliability of its conclusions [29]. Moreover, a disassociation between CVD risk factors and CVD occurrence among study subjects cast a measure of doubt upon the results [29].

Addressing CVD risk in gout and asymptomatic hyperuricaemia

Despite its increasing prevalence, gout remains suboptimally treated. This is, in part, a consequence of poor physician adherence to evidence-based treatments. A study of physician practice patterns relating to three quality indicators at the Minneapolis Veterans Affairs Medical Center found notably low levels of adherence in the management of gout [30]. Analysis of a managed care database found similar results, with two quality indicators measured for physician adherence and found wanting [31]. At the same time, patients’ adherence to their medication regimen has also been shown to be remarkably low [31].

The consequences of suboptimal treatment and poor patient adherence are great indeed when one considers the potential for excess CVD resulting from gout and asymptomatic hyperuricaemia that goes untreated or undertreated. Even where the risk of CVD among these patients may be relatively small, the population in question is so substantial that the potential implications for morbidity and mortality are cause for considerable concern.
Thus, understanding the association of gout and hyperuricaemia with CVD, and evaluating the best available strategies for lowering CVD risk, is potentially meaningful in terms of disease and economic burdens. The remainder of this review will evaluate the current knowledge regarding the pathophysiological link between hyperuricaemia, gout and CVD. It will also examine whether the effects of gout on CVD risk are distinct from those of asymptomatic hyperuricaemia, and whether urate reduction treatment has a meaningful impact upon CVD risk.

Pathophysiological links between gout and asymptomatic hyperuricaemia and coronary artery disease

Gout and hyperuricaemia and inflammation

It is the deposition of monosodium urate crystals (MSUs) in joints and connective tissues that defines the underlying condition of gouty arthritis [32]. The threshold for MSU precipitation, with consequent formation of tophi, is an sUA level of ~6.8 mg/dl [33]. Gout flares occur as a result of these MSU crystal deposits in the joints being suddenly released and setting off an inflammatory cascade that manifests as an acute gouty arthritis attack [34]. Although this acute phase, the gout flare, is self-limiting, Pascal [35] found that MSU crystals remain in the SF, causing persistent low-grade inflammation during the intercritical period. Pascal [35] also observed that MSU crystals will continue to linger in the SF unless a treatment that lowers sUA is applied (and, furthermore, that analysis of SF is diagnostically useful during the intercritical period). A 2007 study by Pascal and Sivera demonstrated that sUA-lowering therapy resulted in the total elimination of MSU crystals in the SF of all 18 gout patients studied. A significant correlation between the time to MSU crystal elimination and duration of gout was observed (P < 0.01) [36]. The presence, and impact, of ongoing inflammatory activity is supported by data from a recent study, which found that MRI and ultrasound imaging revealed erosive changes in the joints during the intercritical period [37].

How, exactly, the flare-related inflammatory cascade occurs, and why, has been the subject of much research and remains incompletely elucidated. Kenneth Rock and colleagues [38] noted that stimulation of the immune system in response to ‘danger signals’, as with infection, is paralleled in the release of danger signals by dying mammalian cells. They observed that uric acid itself is an endogenous danger signal released by injured cells, stimulating dendritic cell maturation and T lymphocytes [38]. These results provide a functional explanation for uric acid as an activator of the immune system. The assumption by Rock and colleagues [38] that the immune response stimulated by release of MSU crystals functioned much like microbial molecules [i.e. via Toll-like receptors (TLRs)] was tested in an in vivo study in which both wild-like mice and mice with TLR deficiencies were injected with MSU crystals and monitored for immune response via neutrophil influx [39]. They found that TLRs were not key to the inflammatory response, but rather that the Toll/IL-1R signal transduction adaptor myeloid differentiation primary response protein 88 (MyD88) is necessary for the inflammatory response [39]. They also demonstrated that IL-1 production and IL-1R activation are central to MSU crystal-triggered inflammation [39]. They determined that the role of MyD88 is as an adaptor molecule in the IL-1R signalling pathway. These data are consistent with a study by Martinon et al. [40], who demonstrated in murine models that after they are released, the MSU crystals engage the inflammasome, a multiprotein complex, resulting in the production of active IL-1β. They found that when mice deficient in caspase-1 or apoptotic speck-like protein containing a caspase recruitment domain (ASC) (components of the inflammasome) were injected with MSU crystals, an impairment in neutrophil influx resulted, implying that MSU crystals mediate the inflammatory process via the inflammasome (Fig. 1; [40, 41]). An inflammatory link between sUA and atherosclerosis related to the IL-1β/IL-1β pathway can be seen, first, in data from Ruggiero et al. [42] showing a linear relationship between sUA and increased IL-1 activity, and secondly, in data from Satterthwaite et al. [43], which demonstrate that IL-1-related aberrations, differential genetic expressions, are seen in the vascular smooth muscle cells in the coronary arteries of patients with advanced atherosclerosis.

Gout and hyperuricaemia and oxidative stress

Urate plays an important role as an antioxidant, scavenging, among other things, peroxynitrite, a toxic formation produced by the reaction of superoxide and nitric oxide (NO) [44]. (In fact, urate scavenges peroxynitrite indirectly by scavenging the radicals produced from the reaction of peroxynitrite and carbon dioxide.) However, urate has a more complex relationship to oxidative stress, possessing both scavenging properties and oxidizing and radical forming properties. In vivo studies have demonstrated that uric acid can induce endothelial dysfunction by exerting anti-proliferative effects on the endothelium and impairing NO production [45–47]. This appears to result from uric acid behaving as a pro-oxidant in vascular cells, increasing lipid oxidization, impairing endothelium-dependent vasodilation and thereby potentially giving rise to CVD risk [45, 48, 49].

Rats have been shown to experience endothelial dysfunction arising from hyperuricaemia, whereas mice lacking endothelial NO synthase experience aspects of the metabolic syndrome [47, 50]. These data support the notion that impaired endothelial cells are releasing less NO, which plays an important role in mediating blood flow, thereby impairing glucose uptake in skeletal muscle [51]. It is worth noting that allopurinol, the standard urate-lowering treatment for gout, was shown in a study from Dundee, Scotland, to improve endothelial function in 11 patients (mean age, 67.5 years; 10 males, 1 female) with chronic heart failure (CHF) [52]. Two later studies from the same source sought to determine the mechanism by which improvements in endothelial function were achieved in CHF patients. (Neither of these studies,
nor the previous Scottish study, involved hyperuricaemic patients.) In the first study, the investigators compared the effects on endothelial function of 300 mg/day and 600 mg/day doses of allopurinol on 30 patients (mean age, 69.7 years; 25 males, 5 females) with mild to moderate CHF. They found that while their urate-lowering effects were similar, and both dosages improved endothelial function (based upon increased forearm blood flow response to acetylcholine) significantly better than placebo (both $P < 0.001$), the higher dose of allopurinol also improved endothelial function significantly better than the lower dose ($P < 0.001$) [53]. In the second study, urate was lowered in 26 patients with mild to moderate CHF (mean age, 67.0 years; 22 males, 4 females) with probenecid treatment at a rate similar to the allopurinol dosages, but this did not result in an improvement in endothelial function [53]. In both studies, ultra-high vitamin C doses were administered to determine the effect of the treatments on oxidative stress. The authors found that while both allopurinol dosages reduced oxidative stress, the higher dose obliterated it altogether; the probenecid had no effect at all [53]. They concluded that the improvements in endothelial function were a result of a reduction in oxidative stress rather than the urate lowering itself [53]. The authors did acknowledge that urate lowering may potentially have a beneficial impact on endothelial function, but if so, it must occur at a higher level than the urate-lowering rate of 44% achieved during their study. It should also be
borne in mind that allopurinol is not a benign drug and that risk–benefit calculations need to be performed before this drug can be recommended for routine use.

In discussing the relationship between gout and oxidative stress in the pathophysiology of CVD, it is important to note the large role played by oxidized low-density lipoprotein (LDL) in the pathogenesis of atherosclerosis. Consumption of oxidized dietary lipids, including oxidized LDL, has been shown in animal models to promote fatty streak lesions in the aorta [54]. In humans, autoantibodies against oxidized LDL are present in elevated levels among patients with coronary artery disease [55]. At the same time, high levels of oxidized LDL antibodies are also seen in patients with gout and can be reduced with urate-lowering treatment [56]. Urate’s dual nature with regard to oxidative stress applies also to its effect on oxidized LDL, against which it can act both as an antioxidant and a pro-oxidant [49]. An in vitro study by Patterson et al. [49] demonstrated that uric acid can play either of these roles depending on the oxidative state of the lipoprotein. They showed that uric acid functioned as an antioxidant in the presence of native LDL taken from human plasma, but in response to mildly oxidized LDL, when the oxidation had occurred via copper, uric acid became a pro-oxidant. Although the mechanism that causes the switch to happen is unclear, it is thought to be related to the availability of lipid hydroperoxides.

Adding to the intertwined picture of inflammation, oxidative stress, lipoproteins and their pathogenic relationship to atherosclerosis is the process of reverse cholesterol transport, the mechanism by which cholesterol, accumulated in vessel walls, is moved to the liver for excretion [57]. Maintaining transport of cholesterol is assumed to reduce atherosclerotic risk, and the failure to do so as a result of inflammation may help to explain part of the deleterious inflammatory influence on CVD. This notion is based on recent data—in murine and human models—showing that inflammation can have a disrupting effect on reverse cholesterol transport [58]. Here, a slightly clearer picture of the interaction between inflammation, oxidative stress and oxidized LDL in promoting atherosclerotic risk can be seen.

**The role of genes**

An understanding of the genetic component of gout and its relationship to atherosclerosis remains an emerging area of research. Genetic loci for uric acid and gout have been identified linking transport proteins to the regulation of sUA levels [59, 60]. Moreover, data from the Framingham Heart Study showed a heritability rate of 63% for sUA levels [61]. Evidence was also seen for pleiotropic effects between uric acid and both BMI and fasting glucose (employed as a surrogate for diabetes). These data are supported by a recent genome-wide analysis of 1955 hypertensive patients, which observed heritability for elevated urate among a patient population already at elevated risk for CVD [62]. The association remained strong after controlling for potentially confounding factors, such as serum creatinine, alcohol use, blood pressure, gender and use of diuretics. The authors of the study [62] noted a common allele within the glucose transporter gene SLC2A9 that increased sUA, a gene that is strongly expressed in the kidneys and liver. However, a potential genetic connection between CVD risk and sUA via SLC2A9 is challenged by a German case–control study that included 665 patients with gout matched with 665 healthy controls. The authors observed a strong association between SLC2A9 (also known as GLUT9) and gout, but observed no significant association with increased risk for coronary artery disease or MI [63].

**Does urate reduction affect cardiovascular function?**

Several pharmacological agents are available for the treatment of hyperuricaemia in gout, including allopurinol and febuxostat, whereas pegloticase, a recombinant, pegylated formulation of a modified mammalian urate oxidase, is under review by the Food and Drug Administration [64–66]. Beyond their proven capacity to lower urate levels, it is of great interest to determine whether they can also lower the risk of CVD. A number of studies in both animal and human subjects suggest that they might.

Induction of hyperuricaemia in rats via the uricase inhibitor oxonic acid was shown to result in hypertension after 3 weeks, whereas blood pressure in a control group of rats remained normal [67]. The hypertensive rats were then either treated with allopurinol or had the oxonic acid withdrawn. In both cases, sUA levels decreased, whereas blood pressure was also reduced. Another study found that after allopurinol treatment, rats with reperfusion-induced arrhythmias experienced significantly less ventricular fibrillation (P < 0.01) as well as a reduction in duration of ventricular fibrillation compared with placebo-treated rats [68]. Similar findings have been reported in studies in which oxypurinol was administered to rats and dogs [69, 70]. However, these data are not entirely consistent. At least two different studies of allopurinol treatment in reperfusion-induced arrhythmias and MI in dogs failed to demonstrate a protective effect, especially in response to more severe periods of ischaemia [71, 72]. Treatment with febuxostat in rats with induced hyperuricaemia (which led to subsequent hypertension) resulted in lowered urate levels and a reduction in blood pressure [73].

In human subjects, allopurinol can—as previously discussed—have a beneficial effect on endothelial function in hyperuricaemic patients. In a study similar to the Scottish studies noted above, hyperuricaemic patients with CHF receiving allopurinol experienced improvements in both vasodilator capacity and blood flow [74]. In patients with CHF who had normal levels of sUA, treatment with allopurinol had no such effects on endothelial function.

Among patients undergoing coronary artery bypass grafting, pretreatment with allopurinol has been shown to reduce lipid peroxidation compared with placebo [75]. Coronary bypass patients treated with allopurinol also showed improved cardiac output recovery compared...
with patients not receiving allopurinol, and whereas both patient groups saw their post-operative sUA levels increase, the effect was significantly attenuated in the allopurinol group (P < 0.05) [76]. These data are, however, undercut to some extent by results from a double-blind, randomized therapy study of 140 patients with ischemic heart disease in which allopurinol increased the incidence of infarct extension [77].

Allopurinol’s capacity to reduce hypertension in hyperuricaemic subjects has been well demonstrated. Kanbay et al. [78] showed a significant reduction (P < 0.05) in systolic and diastolic blood pressure in a 12-week study of 41 hyperuricaemic adults receiving allopurinol (and 18 sex- and age-matched healthy controls). A 4-week study by Feig et al. [79] of hyperuricaemic adolescents with recently diagnosed hypertension also observed significant reductions in systolic and diastolic blood pressure (both P < 0.01) vs placebo.

Allopurinol has further demonstrated beneficial effects in patients with chronic kidney disease. A randomized controlled trial of 54 patients with chronic kidney disease who received either treatment with allopurinol or a continuation of their standard therapy found that the allopurinol patients experienced significant (P < 0.001) reductions in sUA, whereas the control group maintained elevated sUA levels [80]. Simultaneously, the allopurinol-treated patients experienced a slower rate of progression of their renal disease, whereas the control patients deteriorated at a significantly more rapid rate (P < 0.003).

Taken together, these data point to the potential of urate lowering to reduce CVD risk. Whether urate lowering alone would be a sufficient means of reducing increased CVD risk among patients with gout and hyperuricaemia, or whether additional risk reduction targets must also be addressed, remains uncertain.

**Future perspectives**

The primary benefit of understanding the pathophysiological links between gout and atherosclerosis lies in their potential to forward the development of preventive strategies. Lifestyle changes recommended for reducing sUA, such as moderation in diet, exercise and weight loss, have excellent cardiovascular benefits and do not need reiteration here. But what happens when these interventions fail? Patients with gout merit urate-lowering therapies, which are often lifelong in duration. If these interventions turn out to have cardiovascular benefits as well, then the case for a pharmacological approach to gout is that much stronger. Unfortunately, our current understanding of the cardiovascular effects of urate-lowering therapies is based almost exclusively on our experience with allopurinol and thus is too rudimentary to allow for conclusive recommendations. There are, however, several novel urate-lowering treatments, such as pegylated uricase enzyme, febuxostat, Urate transporter 1 inhibitor and a number of other agents in development. These are indeed interesting times for patients, clinicians and researchers in the field of gout.

**Rheumatology key messages**

- An aetiological but multifaceted relationship between CVD risk and gout appears to exist.
- The degree to which reduction of serum urate can reliably improve CVD risk remains uncertain.
- Hopefully, the introduction of novel urate-lowering therapies will improve both gout and atherosclerosis.

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