THE RELEVANCE OF HYPERURICAEMIA

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ABSTRACT

The aim of the present review is to summarise the results from recent clinical studies on the basis of the newly proposed temporal classification of hyperuricaemia and gout, introducing the now evident condition of hyperuricaemia with monosodium urate deposits. Furthermore, it provides an overview of evidence concerning the link between hyperuricaemia and specific pathological conditions, including cardiovascular disease, renal disease, and hypertension.

INTRODUCTION

Endogenous production of uric acid contributes approximately 75% of the body urate pool, the remainder is derived from dietary intake. Characterised by a limited solubility under physiological conditions, monosodium urate can become prone to crystal formation, an event preferentially occurring within cartilage and fibrous tissues that is facilitated by a reduction in temperature. Different epidemiological and clinical studies also support the role of hyperuricaemia with or without urate deposition as a risk factor for a wide spectrum of non-rheumatological conditions. A range of evidence is available to demonstrate the link between hyperuricaemia with or without urate deposition and a wide spectrum of pathological conditions including arterial hypertension, pulmonary hypertension,[1] renal disease,[2] metabolic syndrome, and cardiovascular disease (CVD).[3-7] This review provides an overview of studies concerning the link between hyperuricaemia and specific pathological conditions, including CVD, renal disease, and hypertension.

URIC ACID MEASUREMENT AND HYPERURICAEMIA PREVALENCE

When serum uric acid levels are reduced to <6 mg/dL the deposition of uric acid crystals can be prevented, therefore gout management guidelines (i.e. European League Against Rheumatism [EULAR], American College of Rheumatology [ACR]) advise to treat to a target <6 mg/dL in the chronic treatment of the disease.[8,9]

This rising prevalence of hyperuricaemia in recent decades, which is reflected by the concomitant increase of gout incidence, has been ascribed to the Westernisation of diets, malnutrition, and the use of certain medications, mainly including diuretics, acetylsalicylic acid, and ciclosporin, the latter of which is known to reduce the renal clearance of urate.[10,11]

THE RELEVANCE OF HYPERURICAEMIA FOR CARDIOVASCULAR RISK EVALUATION

Hyperuricaemia with or without urate deposition has been found to be frequently associated with CVD. Indeed, a recent meta-analysis of 35 studies involving almost 100,000 patients showed that hyperuricaemia is a risk factor for incident hypertension.[12] More recently, large amounts of data from the Chinese Cohort Study, involving 93,393 participants (~50% males) demonstrated that hyperuricaemia was an independent risk factor of mortality from all causes, total CVD, and ischaemic stroke. This correlation was more significant

in women than men. This study also found a linear relationship between serum urate (SUA), and all-cause and CVD mortality.[13]

In patients at high risk of CVD, elevated SUA level is an independent predictor of death. For each 1 mg/dL increase of SUA concentration, a rise in the risk of death for all causes of 39% has been reported.[14] The association was stronger in patients with a positive history of coronary artery disease. After adjusting for age, sex, smoking status, alcohol intake, weight, body mass index, waist circumference, blood pressure, history of CVD, estimated glomerular filtration rate (eGFR), cholesterol fractions, and plasma glucose levels, SUA levels continued to be strongly predictive of the risk of death (hazard ratio: 1.26, 95% confidence interval: 1.15–1.38). Prolonged elevation of SUA levels has been found to be associated with peripheral vascular disease, and long-standing elevated SUA levels are predictive of worse outcomes after an acute stroke over 2 years, independently of other comorbidities.[15]

In humans, studies regarding hyperuricaemia and the development of hypertension have generally been consistent, continuous, and of similar magnitude, and epidemiological studies have demonstrated that hyperuricaemia carries an increased relative risk for hypertension within 5 years, independent of other risk factors.[16] Further evidence supporting the pathogenetic role of hyperuricaemia was found in the reduction of both systemic and glomerular pressures occurring with the normalisation of SUA levels provided by febuxostat in rats with oxonic acid-induced hyperuricaemia. Treatment with febuxostat also reduced and alleviated afferent arteriolar thickening, mesangial matrix expansion, and the development of pre-glomerular arteriolar disease. In normal rats, febuxostat lowered SUA levels without any effect on blood pressure, renal haemodynamics, or afferent arteriole morphology.[17]

According to recent hypotheses about the pathogenetic steps in the development of hypertension induced by hyperuricaemia, uric acid has been hypothesised to have a role in driving intracellular oxidative stress, endothelial dysfunction, renin-angiotensin-aldosterone system activation, and reduced nitric oxide (NO) bioavailability (Figure 1).

The intracellular oxidative stress may induce mitochondrial alterations and decrease endothelial NO bioavailability, and also activate the RAS and increase endothelin levels. The net effect is to induce renal and systemic vasoconstriction and the development of hypertension.[18,19] Data from some studies in humans observed that the lowering of urate levels may be beneficial for vascular function by reducing oxidative stress.[20,21]

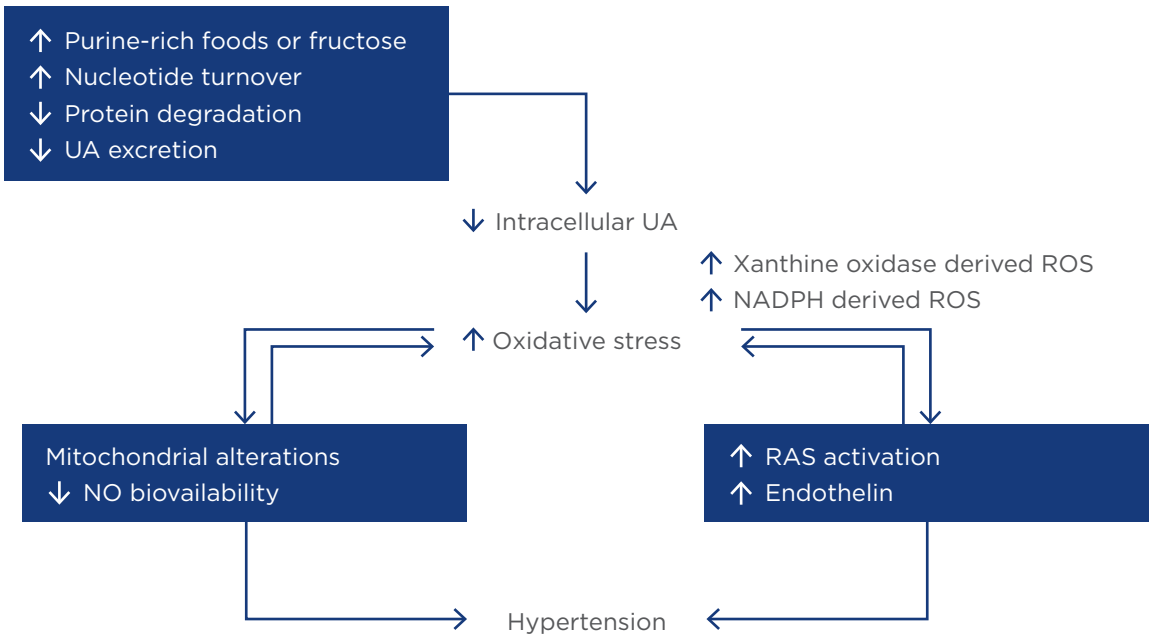

Figure 1: A model for the explanation of the pathogenetic role of hyperuricaemia in hypertension.
UA: uric acid; ROS: reactive oxygen species; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide.

Table 1: Change in estimated glomerular filtration rate from baseline by change from baseline serum uric acid.[27]

		Mean Change in SUA from baseline (mg/dL)														
		≤3			>3 to ≤4			>4 to ≤5			>5 to ≤6			>6		
		n	Mean (95% CI)	SD	n	Mean (95% CI)	SD	n	Mean (95% CI)	SD	n	Mean (95% CI)	SD	n	Mean (95% CI)	SD
eGFR (mL/min)	Baseline eGFR	19	67.3	15.31	17	71.1	14.07	32	65.7	9.18	21	67.9	13.39	26	59.5	13.10
	Change Year 1	19	-2.2 (-4.8–0.4)	5.39	17	-0.4 (-5.5–4.8)	10.02	32	0.5 (-2.1–3.1)	7.20	21	-1.4 (-6.4–3.6)	10.96	26	2.0 (-1.3–5.3)	8.19
	Change Year 2	11	-3.6 (-8.7–1.4)	7.54	11	-4.8 (-9.2– -0.4)	6.59	24	2.8 (0.2–5.4)	6.19	18	-3.7 (-9.1–1.8)	10.98	19	4.3 (0.5–8.2)	8.01
	Change Year 3	8	-4.6 (-11.3–2.1)	8.03	8	-2.8 (-6.8–1.3)	4.80	22	-1.5 (-4.6–1.7)	7.09	16	-6.7 (-14.6–1.3)	14.90	17	-0.3 (-5.2–4.6)	9.54
	Change Year 4	7	-8.4 (-18.4–1.5)	10.77	8	-0.5 (-6.3–5.3)	6.97	21	-1.7 (-5.5–2.2)	10.52	14	-2.9 (-6.5–0.8)	6.40	16	2.3 (-2.5–7.0)	8.83
	Change Year 5	5	-10.8 (-19.6– -2.0)	7.05	8	-2.0 (-7.9–3.9)	7.01	19	-1.5 (-6.6–3.5)	10.52	14	0.6 (-5.7–7.0)	11.04	14	0.5 (-4.5–5.5)	8.59

eGFR: estimated glomerular filtration rate; SUA: serum uric acid; CI: confidence interval; SD: standard deviation.

HYPERURICAEMIA AND CHRONIC KIDNEY DISEASE

More than 50% of patients with gout have some degree of renal insufficiency and nearly 100% had renal disease at autopsy.[16] Large studies like the National Health and Nutrition Examination Survey (NHANES)[22] and the German Chronic Kidney Disease (GCKD) Study[2] show an increase in the incidence of hyperuricaemia in parallel with the decline in eGFR. In addition to this impressive association between impaired renal function, data from 18 prospective cohort studies in 431,000 patients revealed that hyperuricaemia predicts the occurrence of chronic kidney disease (CKD) as well as the rate of decline in renal function.[23] Interestingly, elevated SUA levels have also been found to be an independent predictor of the development of microalbuminuria in diabetes, a surrogate of kidney damage.[24]

How Does Hyperuricaemia Lead to Renal Damage?

Histopathologic findings in the kidneys of patients with gout are mainly characterised by advanced arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis. It therefore seems that microvascular damage plays an important role in the development of renal impairment due to hyperuricaemia, rather than the classical interstitial nephritis with urate crystal deposition.

Based on data from a large patient population with hyperuricaemia (N=16,186),[25] it was found that subjects achieving SUA <6 mg/dL with urate-lowering therapy are 37% less likely to have renal disease progression. Hence, based on the epidemiological and preclinical data, hyperuricaemia plays an important role in the development of both impaired renal function (decline in eGFR) and of renal damage, i.e. proteinuria. If this paradigm is true, lowering uric acid should have an effect on renal function as well as on renal damage, i.e. proteinuria.

URATE-LOWERING THERAPY IN CHRONIC KIDNEY DISEASE

The Febuxostat Open-label Clinical of Urate lowering efficacy and Safety (FOCUS) study enrolled 116 hyperuricaemic gout subjects receiving daily doses of febuxostat (40, 80, or 120 mg) for up to 5 years with regular assessment of SUA levels and eGFR. In this cohort of patients a *post hoc* analysis clearly demonstrated the correlation between maintenance or improvement in eGFR and the quantitative reduction in SUA levels from baseline. For every 1 mg/dL decrease in SUA concentration, the model projected an expected

improvement in eGFR of 1 mL/min from the untreated value.[26] These results were further confirmed by an analysis of two Phase III studies, considering the subjects who received only febuxostat throughout the duration of the studies (n=551). Greater sustained decreases in subjects' SUA levels were associated with a smaller decline in renal function (p<0.001), as shown in Table 1.[27]

A consensus document for the detection and management of CKD published by the Spanish Scientific Societies reported that in patients with symptomatic hyperuricaemia and mild-to-moderate renal failure, febuxostat administration had demonstrated greater efficacy and a similar safety to allopurinol, without the need to adjust the dose.[28]

CONCLUSIONS

Hyperuricaemia has been found to be associated with a wide spectrum of non-rheumatological conditions. Results of several animal and human studies have clearly demonstrated the link between hyperuricaemia with or without deposition and a wide spectrum of pathological conditions, including CVD, arterial hypertension, pulmonary hypertension, and CKD.[7]

The life-long risk of developing gout has been reported to arise with SUA concentration above 6 mg/dL, which represents the limit rationally proposed for a definite, evident, and universally accepted definition of hyperuricaemia. Lowering SUA levels could produce cardiovascular and renal benefits. This appears likely to be related to the overproduction of reactive oxygen species and vascular inflammation sustained from increased SUA levels (blood vessels) as well as increased renin production and reduced NO levels with interstitial fibrosis and inflammation (kidney).

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