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## *Leaders*

# Hyperlipidaemia in hyperuricaemia and gout

The finding of hyperlipidaemia in patients with hyperuricaemia and gout is common. The usual abnormality is hypertriglyceridaemia (type IV hyperlipoproteinaemia),[1 2] being reported in between 25% and 60% of patients with gout.[3 4] This finding has been related to reports of an increased frequency of coronary artery disease in some patients with gout and has contributed to the suggestion that the urate concentration might be an indicator of coronary risk. Now that gouty arthritis itself is so treatable, an associated disorder that might reduce the life span becomes even more important in the management of a patient with gout.

However, our understanding of the mechanism of any association between hypertriglyceridaemia and hyperuricaemia is far from complete and this becomes increasingly important when determining the factors that contribute to the development of hyperuricaemia and gout in a particular person. No longer can it be assumed that there is a common aetiology for the hyperuricaemia in patients who present with an acute urate crystal arthropathy and refer to it as "primary gout". Similarly, it is no longer expected that each patient with gout would have inherited a "gouty diathesis", unless you regard this concept as meaning a relatively poor renal clearance of urate in the presence of otherwise normal renal function.[5] Hyperuricaemia in most patients is found to have multiple causes, some genetic and others environmental, with many of the latter being able to be modified, potentially correcting the contribution of that cause to the hyperuricaemia.[6 7]

In such an assessment, the contribution of each factor to the hypertriglyceridaemia may also need to be considered and a series of inherited and environmental factors have been sought. Of the genetic causes, an uncommon allelic variant of the apoprotein CIII gene (the S2 allele) was found to be more common among a group of hypertriglyceridaemic patients with gout[8] and, more recently, a higher frequency of an apo e4 allele has been found in such patients.[9] That such a search revealed relatively so little suggests that the association between the hyperuricaemia and hypertriglyceridaemia is not predominantly genetic. Of the other factors that might contribute, the two obvious ones are obesity and alcohol consumption,[10] and there is good evidence that each of these, in appropriate individuals, can and does contribute to both hypertriglyceridaemia and hyperuricaemia. Obesity, especially abdominal obesity,[11 12] and excessive weight gain in young adulthood,[13] have been associated with an increase in both the urate and triglyceride concentrations. Likewise, alcohol consumption is well established as a factor that can contribute to both hyperuricaemia and raised triglyceride concentrations.[14 15] However, while obesity and alcohol consumption are the commonest causes of the hyperuricaemia/ hypertriglyceridaemia association, there are still numbers of patients in whom neither of these is the apparent aetiology.[16 17] There is also some support for a contribution from disturbed carbohydrate metabolism in gouty patients with hypertriglyceridaemia and in some of these patients, impaired glucose tolerance and excessive insulin secretion has been found.[16]

The possibility that hyperinsulinaemia might be an important contributor to dyslipidaemia as part of a more fundamental metabolic disorder that might promote the development of vascular disease was developed by Reaven into the concept of a metabolic syndrome in which hyperinsulinaemia and resistance to the effect of insulin on carbohydrate metabolism is the fundamental problem.[18] Other commonly associated features of this syndrome include an increase in the body mass index and the waist/hip ratio (abdominal obesity), impairment of glucose tolerance, hypertriglyceridaemia, an increase in apolipoprotein B and small dense LDL cholesterol and a reduction in HDL cholesterol. In this syndrome, clustering of the various adverse cardiovascular risk factors is common, including an association with hypertension and the development of coronary artery disease.[19 20] Endothelial dysfunction has also been described in insulin resistant subjects and this may be the mechanism for the associated increase in the risk of atherosclerosis.[21]

The insulin resistance syndrome may present clinically in many different ways, particularly as impaired glucose tolerance with moderate increase in the fasting blood sugar. It may also present as hypertension or as hyperlipidaemia with myocardial ischaemia.[22 23] Now that hyperuricaemia has come to be recognised as an intrinsic part of the syndrome,[20] it is being realised that one of the clinical presentations may be as gouty arthritis. Indeed, the degree of hyperuricaemia has been proposed as a simple marker of the degree of insulin resistance.[24] The renal clearance of urate has also been shown to have an inverse relation with both the degree of insulin resistance[25] as well as with visceral fat area as measured by abdominal computed tomography.[26] Thus, as we look more closely at some of

our patients presenting with gout, we are increasingly recognising the presence of other features of this syndrome. The perception of this insulin resistance syndrome really depends upon the perspective from which its presentation is viewed. When the presentation is as gout, you usually find evidence of the associated hypertriglyceridaemia or impaired glucose tolerance or hypertension only if you seek it specifically. Also, a clinical presentation as acute gout may well occur earlier than one resulting from complications from other components of the syndrome, which may be asymptomatic for years.

Many studies have examined different aspects of the relation between the manifestations of the insulin resistance syndrome, studying different types of subjects and using different study techniques.[23 25 27–29] A consensus is emerging that hyperuricaemia is an intrinsic component of the syndrome and that this hyperuricaemia is caused by a reduction in the renal clearance of urate leading to underexcretion of urate. There has been no clear evidence that the syndrome incorporates a component of overproduction of urate. The recent demonstration that exogenous insulin can reduce the renal excretion of both urate and sodium in both healthy and hypertensive subjects[28 30] provides a ready mechanism to explain the association of hyperinsulinaemia with hyperuricaemia and hypertension, especially if the kidney retains its sensitivity to the effects of insulin at a time when other organs are insulin resistant. Dietary reduction of the triglyceride concentration with a low calorie diet increases renal excretion of urate in hyperuricaemic hypertriglyceridaemic subjects, but the effect is reversed when the triglycerides are again increased.[31] Differences in renal handling of urate as a response to calorie restriction and weight loss have also been shown in hyperuricaemic subjects with hypertriglyceridaemia from those with only hyperuricaemia.[31] This would be explicable if only those with hypertriglyceridaemia were to have hyperinsulinaemia.

Although the syndrome is well defined clinically, its basic pathogenesis is still not completely clear.[32] However, it is generally agreed that the serum urate, while it is highly correlated with risk factors for vascular disease, is unlikely itself to be the contributor to any associated atherosclerosis.[33] Perhaps most important from the perspective of the patient with gout is the recognition that, in the presence of the insulin resistance syndrome, the hyperuricaemia usually originates from a reduced renal excretion of urate.[25]

Insulin resistance now needs to be recognised and treated as a potentially more life threatening factor than hyperuricaemia and gout. Abdominal obesity, suggested by a waist circumference exceeding 100 cm, should alert one to the possibility. Once recognised, insulin resistance may be managed either by non-pharmacological interventions such as exercise and a high monounsaturated fat diet or, if there is sufficient impairment of glucose tolerance, by the use of drugs to increase insulin sensitivity.[34] All who see patients with gout now need to look beyond their gout to determine the extent of any associated risk of vascular disease.

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