Gout

Gout, diuretics and the kidney
E Pascual, M Perdiguero

Occurrence of gout may depend on the condition for which diuretics are prescribed rather than resulting from the drugs themselves

Gout is a monosodium urate crystal deposition disease. Formation of the crystals requires high serum uric acid levels; the local factors responsible for their predilection for the joints are only started to be grasped.\(^1\) Steady serum urate levels result from the balance between its production and excretion; hyperuricaemia results when formation is increased or difficulties in (mostly) renal excretion occur. In humans, urate is the final breakdown product of purine nucleotides, constituents of cellular energy stores such as ATP, and of DNA and RNA both internal or, to a lesser extent, ingested.

Increased urate formation is the cause of hyperuricaemia and gout in some well defined enzymatic defects, and also occurs as a consequence of increased destruction of cells in some malignancies, polycythaemia vera or some haemolytic anaemias. Patients with increased production of urate are classified as overproducers, and detection of an increased amount of excreted urate is considered to be a good method of detecting the few patients whose gout results either from enzymatic defects—which are partial in the adult—or a tumour or other condition with a rapid cellular turnover.\(^1\)

Two thirds of urate excretion occurs at the kidney, the remainder being excreted by the gut. In an estimated 85–90% cases, gout results from poor renal disposal of urate. Gouty patients with normal or low excretion of uric acid (underexcretors) may be candidates for treatment with uricosuric drugs with little risk of urinary calculi. Measurement of the amount of excreted urate has also been recommended to identify these patients.

Measurement of the amount of excreted uric acid has been considered to have clinical implications. However, although on most occasions hyperuricaemia results from poor urate clearance in otherwise normal kidneys, its calculation appears to have little use for patient management and has received little attention in the clinical setting. But this measurement is often informative, explaining why many gouty patients develop their disease.

Understanding the renal handling of urate is important to understand why some drugs cause hyperuricaemia. The renal excretion of urate is the result of tubular secretion and reabsorption of urate. The relative amounts of urate being secreted and reabsorbed may be assessed by the measurement of fractional excretion of urate.

Fractional excretion of urate helps us to understand the normal or altered urate levels in a number of circumstances. Thus the lower serum urate levels of women, which are at least partially explained by their higher fractional excretion of urate\(^1\) and by the increase in urate levels from prepubertal to pubertal girls, coincides with a decrease of their fractional excretion of urate.\(^2\) By contrast, the lower uricaemia which gouty patients present during gouty attacks is due to a higher fractional excretion of urate,\(^2\) and the very low uricaemia which may accompany jaundice, some solid haematological tumours, diabetes or intracranial diseases, results from a very high fractional excretion of urate leading to inappropriate uricosuria.\(^3\)

Difficulty in renal urate excretion is also responsible for hyperuricaemia and gout. These are associated with a number of common situations, such as the metabolic syndrome\(^4\)—which is correctable by changing to a low caloric diet\(^5—\)essential hypertension,\(^6\) decompensated heart failure,\(^7\) satiﬁringe gout—which is correctable by lead chelation\(^8—\)alcohol consumption. Hyperuricaemia and gout also occur as a result of the ingestion of different drugs such as ciclosporin\(^9\) or low dose aspirin,\(^10\) and of which, diuretics are the most widely prescribed. A low fractional excretion of urate has also been found in patients with high 24 h uric acid excretion.\(^10\) Establishing how the kidney handles urate by calculating the fractional excretion of urate, or the urate clearance, may be of little use in choosing a hypouricaemic drug, but can help us to understand the reason for a patient’s hyperuricaemia.

Hyperuricaemia is a widely publicised consequence of diuretic treatment, such that in the current guidelines on the management of hypertension, having gout is considered as a contraindication for the administration of diuretics.\(^11,12\) Diuretics induce hyperuricaemia by increasing urate reabsorption, though the exact mechanism has not been elucidated. It has been noted that hyperuricaemia occurs when diuretics produce sufficient salt and water loss as to result in volume contraction; this

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stimulates solute reabsorption at the proximal tubule,24 25 and this effect is corrected by administration of the lost fluid.26

Different diuretics are likely to have different effects on the renal handling of urate, but this has not been critically ascertained; patients receiving more powerful loop diuretics have a higher risk of developing gout than those receiving the weaker thiazides.27 Interestingly, bumetanide has been found to have uricosuric properties.28

“Renal handling of urate depends on the type of diuretic used”

In this issue of the Annals, Janssens et al report that in their gouty patients who received diuretics their gout related to the condition for which the diuretics were prescribed, rather than resulting from the drugs themselves.29 These data were prescribed, rather than resulting from the drugs themselves.29 These data were prescribed, rather than resulting from the drugs themselves.29 These data were prescribed, rather than resulting from the drugs themselves.29 These data were prescribed, rather than resulting from the drugs themselves.29 These data were prescribed, rather than resulting from the drugs themselves.29


Hopkinson N, Doherty M. In patients with chronic cardiac failure who have diuretic induced gout, are certain diuretics less prone at causing problems? Br J Rheumatol 1991;30:225.


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