Genes, fructose, allopurinol and gout

Gout affects approximately 15% of Pacific men and 3% of Pacific women. This is a similar prevalence to that in Māori, however five-fold more than in people of European ethnicity. Pacific peoples also have high rates of severe gout, early onset gout, tophaceous disease and accelerated joint damage.[1] A major factor in the high incidence of gout in Pacific peoples is inherently higher levels of serum urate (hyperuricaemia). Current evidence indicates that hyperuricaemia and gout have both a genetic and environmental basis.

A genetic basis for hyperuricaemia

Recent genetic data show that genes that encode proteins responsible for excretion of urate via the kidneys and gut are strong risk factors for gout in Pacific peoples. A genetic variant in the SLC2A9 gene confers a greater than five-fold increased risk for gout in Pacific peoples,[2] and a genetic variant in the ABCG2 gene confers a three-fold increased risk of gout.[3] It is thought that these genetic variants reduce the ability to excrete urate, contributing to hyperuricaemia and thus the risk of gout. This genetic information is consistent with biochemical data from the 1980s that demonstrated reduced renal clearance of urate in Pacific peoples when compared to people of European ethnicity.

Dietary influences in hyperuricaemia with particular reference to fructose

It is well recognised that certain foods, e.g. alcohol, meat and shellfish, contribute to hyperuricaemia. Recent studies in North America have shown that soft drinks sweetened with high fructose corn syrup, but not artificially sweetened soft drinks, are also associated with hyperuricaemia and gout.[4, 5] This effect of increasing serum urate was also seen with fruit juice and excessive consumption of fruit. Fructose is a component of refined sugar, but in contrast

to glucose, the metabolism of fructose in the blood is not regulated. Therefore fructose cannot be stored in the body, in the way glucose is stored as glycogen in the liver. An adverse effect of the unregulated catabolism of fructose is the production of urate in the blood, increasing the risk of gout in people who are genetically predisposed to excrete less urate.

Patients with gout, particularly Pacific patients, should be advised to drink water, unsweetened coffee and tea, and milk rather than fruit juices and sugar-sweetened soft drinks. Low fat dairy products such as milk have been shown to be associated with lower serum urate levels and reduced risk of gout.[6] In patients with poorly controlled gout, excessive fruit intake should also be advised against. A healthy diet including recommended serves of fruit and vegetables should be recommended.

High fructose consumption is also implicated in hypertension. A clinical study has shown that concurrently lowering uric acid levels with allopurinol prevents an increase in arterial blood pressure.[7] The authors of the study postulated that excessive fructose intake also has a role in the current obesity and diabetes epidemic.[8]

The role of allopurinol in the management of gout

Allopurinol is the most commonly used drug for the long-term management of gout. It inhibits the enzyme xanthine oxidase, which is responsible for the production of urate. It can be difficult to establish patients on allopurinol, as it often precipitates gout flares. However, concurrent administration of colchicine, non-steroidal anti-inflammatory agents or corticosteroids in the first three to six months is an effective strategy for preventing gout flares.

Sustained reduction of serum urate <0.36 mmol/L is critical for the long-term management of gout. It may take 6–12 months of serum urate levels <0.36 mmol/L before gout attacks abate. In general, creatinine clearance (CrCL) based doses of allopurinol are used in an attempt to reduce potential adverse effects, in particular allopurinol hypersensitivity syndrome. However, many patients fail to achieve the target serum urate (<0.36 mmol/L) with CrCL based doses.[9] In renal impairment, reducing the dose of allopurinol does not increase its safety.

The effects of increasing the dose of allopurinol above CrCL based doses in patients who fail to achieve reduction in serum urate to <0.36 mmol/L has recently been investigated in a New Zealand based study.[10] The dose of allopurinol was gradually increased until the target serum urate was achieved. The dose of allopurinol required to reach the target ranged from 50–400 mg above the CrCL based dose. All but one patient (34 out of 35) achieved a serum urate <0.36 mmol/L at some stage during the study period and in 31 patients this was sustained. There were no significant adverse effects during the twelve month study period. Although larger studies are required for confirmation of the safety of such an approach, treating with allopurinol to achieve the target serum urate appears safe and effective.

"Treat to target"

From a practical perspective it is recommended to gradually build up to the CrCL based dose of allopurinol. If this fails to achieve the target serum urate after four to six weeks, the dose of allopurinol should be systematically increased until the target serum urate of <0.36 mmol/L is reached unless adverse events occur. This "treat-to-target" approach is being increasingly practised and accepted.

Other urate lowering therapies

Other urate lowering therapies which increase the excretion of urate via the kidneys are available. Benzbromarone is one such agent which exerts its effects through the SLC2A9 urate transporter in the kidney. Benzbromarone may be a more effective therapy for Pacific peoples with gout who under-excrete urate, however it is not currently registered for use in New Zealand.

For further information about the treatment of gout, see; "Gout – hit the target", BPJ 8 (Sept, 2007) and "Gout in the Māori community", BPJ 13 (May, 2008).

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