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REVIEW

Gout

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Introduction

Gout is an inflammatory arthritis that can be monoarticular or polyarticular. It manifests as an acute, sub-acute or chronic condition and often mimics other medical diseases. It can evolve over time, both in frequency, severity and involved sites. It can co-exist with other medical problems and can be difficult to treat. However, gout is often poorly treated and patients are often poorly educated about the disease process. As a result, patients often have significant impairment in their quality of life and are at risk from complications due to excess use of anti-inflammatories in an attempt to quell their pain. There are many myths surrounding both the causes and treatment of gout and, hopefully, this article will help to dispel some of these. At the end of this document, there are some links to sites that may be helpful to both patients and their doctors. The presence of guidelines for the treatment of gout allows goals to be met with a greater chance of treatment success and reduced chance of long-term joint damage.[1] These guidelines highlight the need for regular checking of serum uric levels and adjustment of treatment dosage until the **treat-to-target goal** is met. Patients often do not realise that gout is an arthritic process and that as such, poor disease control may result in multiple possible poor outcomes. Gout is the result of deposits of monosodium urate (MSU) crystals in joints or other structures.[2] The crystallisation occurs when the hyperuricaemia exceeds the solubility level (analogous to a dam overflowing with water). This may occur chronically or intermittently. The frequency of acute attacks gradually increases over time.[3]

Case scenario

Mr XY, suffering from gout, was referred by his general practitioner. Mr XY says he first had an attack of gout at the age of 32. His father also suffered from gout. Mr XY's gout was proving difficult to treat. Various dietary interventions have not alleviated the increasingly frequent gouty episodes. He says he did try using allopurinol some years before the consultation, but thought that his attacks became more frequent with the introduction of allopurinol. As a result, he stopped taking it and reverted to using acute "gout packs" as needed. He had not had his renal function or serum uric acid checked for a few years. A review of previous blood chemistry results confirmed a high serum uric acid level many years previously, and a normal glomerular filtration rate. He was fully educated about the difference between the treatment of acute gout and the long-term prophylactic treatment of gout with allopurinol. He was advised to start with a very low dose of allopurinol and increase this very gradually over a couple of months with additional acute medication as required. He was not to stop his allopurinol (except if he developed an allergic skin rash) even if he developed an acute episode of gout after starting it. He was advised that, over time, if he persevered with the allopurinol and adjusted the dose upwards to achieve a goal serum uric acid of 0.35 mmol/L or less, he would notice that the frequency of acute attacks would gradually decrease as would the size of his tophi. Mr XY, in turn, said that he had not previously understood the importance of persevering with the Puricos and the need for gradual dose titration to achieve his goal. He was relieved to hear that he did not have to depend on dietary intervention alone, especially as he had read so many conflicting reports about what he could or could not eat.

At his three-month review, he had managed to increase his allopurinol to 300 mg daily and serum uric acid was nearly at goal. He had become adept at using anti-inflammatories, colchicine and prednisone as required and was maintaining good levels of water intake. He felt more positive and in control going forward.

What is the difference between hyperuricaemia and gout?

Part of the gout enigma for physicians is that not all patients with hyperuricaemia will develop acute gout.[4,5] Only up to 36% of those with hyperuricaemia develop gout, while some patients with gout can have normouricaemia. Additionally, the introduction of allopurinol may pose risk in terms of side-effects to some patients, hence, ideally, one would like to treat those where the risk/benefit ratio is highest. The progression from asymptomatic hyperuricaemia without crystal deposition to crystal deposition without symptomatic gout, to acute gout flares and tophi, and then to chronic gouty arthritis is not clearly defined. However, the chances of developing gout in the future are increased when serum uric acid levels rise. Uric acid (UA) is the catabolic end-product of both exogenous and endogenous purine nucleotide metabolism in humans – this explains both why those with higher muscle mass (males) and those with high protein intake may develop gout.

Recommendations for initiating urate-lowering therapy (ULT) is strongly recommended for gout patients with any of the following:

- ≥ 1 subcutaneous tophi
- evidence of radiographic damage (any modality) attributable to gout, and
- frequent gout flares, (defined as ≥ 2 annually)[1]

Special consideration should also be given to all patients with impaired renal function and even a single episode of gout, as the risk for further acute attacks is high. However, though it presents as an intermittent clinical picture, gout is in fact a chronic disease.

Several trials have suggested that lowering the serum uric acid level is associated with a slowing in the rate of renal deterioration in those with chronic kidney disease. This was the meaning of the term gouty nephropathy. The only angiotensin receptor blocker (ARB) in studies that reduced serum uric acid levels was Losartan, and a post hoc analysis of the trial on Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the angiotensin II antagonist Losartan (RENAAL) showed that the uric acid-lowering effect of Losartan was associated with long-term renal risk reduction.[6]

Risk factors for hyperuricaemia

Hyperuricaemia can be attributed to several genetic variants – 43 genes being identified to date.[7] The younger the age of the patient presenting with definite gout, assuming normal renal function, the more likely it is that genetic mechanisms are contributing to the aetiology. UA is the end catabolic product of exogenous and endogenous purine nucleotide metabolism in humans.

High UA levels have been linked to lower eGFR, obesity, hypertension, dyslipidaemia and fatty liver disease. Patients with gout need to be managed holistically with attention to associated risk factors and aggressive lifestyle intervention and medication where appropriate.

How to diagnose gout correctly

Gout can be notoriously difficult to diagnose. The definitive confirmation of the presence of gout is the finding of crystals on fluid aspirated from a joint subjected to polarised light microscopy. Newer means of confirming the presence of gouty crystals on ultrasound or with dual-energy computed tomography (DECT) have allowed non-invasive options to be considered. MRI features are non-specific, but may be helpful to monitor response to treatment. A good history from the patient, combined with thoughtful review of risk factors, is still key to placing gouty arthritis in the differential diagnosis of joint pain.

The difference between symptomatic and prophylactic management of gout

While treatment of acute attacks of gout provides short-term relief, recurrent "spill-overs" of UA crystals can lead to irreversible damage over time, both intra- and extra-articularly. Extra-articular crystals may contribute to multiple comorbidities (e.g. renal disease) and intra-articular damage may cause a very destructive arthropathy that is both irreversible and has a significant impact on quality of life.

Why adequate reduction of uric acid is the key in the long term

As mentioned above, a sustained and well-documented decrease in serum uric is the only definitive way to prevent long-term joint damage. Unless patients understand that their urate-lowering therapy (ULT) is chronic and indefinite, they will be tempted to reduce or stop it as soon as they become asymptomatic. Patient compliance with ULT is the only way to prevent joint damage and reduce the frequency of acute attacks. The lower the serum uric acid, the less the chance of having an acute flare – bearing in mind that when treatment with allopurinol commences, it will lower serum uric acid first, and then resorb gouty crystals from joints or soft tissues. This can take a much longer time, and the time to full resorption correlates with past duration of gout and the burden of crystal deposition.

The many different faces of gout

While the great toe (1st MTPJ) is the well-known classical affected joint in acute gout, many other sites, such as the hyaline cartilage surface and tendons, ligaments, retinacula and bursae in peri-articular soft tissues, may also be affected when hyperuricaemia occurs. Gout can also affect the axial skeleton, although it usually affects peripheral joints.

Factors contributing towards gout

Obesity, high blood pressure, cardiac failure and diabetes are all linked both causally and as a consequence of the elevated serum uric acid.

Factors contributing towards acute gouty flares

Dehydration, reduced glomerular filtration rate, certain antibiotics (Co-amoxiclav), high purine intake, alcohol and pre-existing UA crystals (secondary nucleation) have all been linked to acute gouty episodes. Osteoarthritis or other causes of cartilage damage may act as a nidus for new crystals, explaining why gout attacks often occur at previous injury sites.

Medication linked to gout

Medications linked to gout include some diuretics, β-blockers, angiotensin-converting enzyme inhibitors, non-losartan angiotensin II antagonists, cyclosporine, tacrolimus, and low-dose aspirin. If possible, thiazide diuretics should be replaced with an alternative antihypertensive agent in patients suffering from gout. While low-dose aspirin may aggravate gout, cardiac safety should take precedence over the contribution of low-dose aspirin towards the causation of gout. Losartan would be an antihypertensive of choice for those with gout.

The role of diet in managing gout

Diet's role in managing severe gout is relatively small when compared with the potency of uric acid-lowering drugs.[8] Weight reduction is important in both prevention and treatment, but there is no single diet that can be used definitively to treat gout. As gout is often linked to other metabolic syndromes, attention

should be given to dietary intervention of these associated conditions.[9]

Patient and doctor support links

https://gouteducation.org

https://gouteducation.org/wp-content/uploads/2023/10/Gout_Patient_Booklet-2023.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10563586

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