TREATMENT OF GOUT

HIT THE TARGET

KEY ADVISER

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www.bpac.org.nz Keyword: ***"Gout"***

SUMMARY POINTS

1. ***Gout is a major cause of arthritis in New Zealand, with high rates of severe disease in Māori and Pacific patients***
2. ***Gout causes significant disability in Māori and Pacific men of working age***
3. ***All patients with gout should have cardiovascular disease (CVD) risk assessment, and intensive management of modifiable risk factors***
4. ***Long-term preventive therapy with allopurinol is critical for effective gout management:***
   - *Prescribe early, before development of tophi*
   - *Monitor serum uric acid levels*
   - *Aim for target serum uric acid <0.36 mmol/L*
   - *Introduce gradually: 'start low and go slow'*
   - *Use colchicine prophylaxis*
5. ***Minimise diuretic therapy in patients with gout***

WHAT IS GOUT?

Gout is an arthritis caused by the inflammatory response to intra-articular monosodium urate crystals. Supersaturation of urate typically occurs in physiological fluids above concentrations of 0.42 mmol/L. In early disease, gout presents as recurrent episodes of self-limiting acute inflammatory attacks ('flares') of arthritis. These attacks most often affect the 1st metatarsophalangeal joint, midfoot and ankle. In the presence of prolonged hyperuricaemia, some patients develop recurrent polyarticular attacks, chronic tophaceous disease, erosive arthritis (images are available in the online version of this article visit www.bpac.org.nz) and renal disease (urate nephropathy and uric acid stones).

NATURAL HISTORY OF GOUT

If untreated, the evolution of gout follows four stages:

1. ***Asymptomatic hyperuricaemia*** – asymptomatic hyperuricaemia has traditionally remained untreated with drugs. Although evidence is building, linking hyperuricaemia with cardiovascular and renal disease, treatment remains unproven. Identification of hyperuricaemia presents an opportunity to suggest diet and lifestyle changes to patients and also to look for possible underlying causes for the raised uric acid. Of those with hyperuricaemia, 20% will go on to develop acute symptomatic gout.

2. ***Acute attacks*** – typically the first attack involves one joint but it can also be polyarticular. Without specific treatment, an attack of acute gout is likely to resolve within 7–10 days. In practice, the severe pain usually forces patients to seek pharmacological relief.

3. ***Intercritical gout*** – the length of time between attacks can vary widely. Some patients only ever have one attack, but for the majority, a second attack will occur within a year. If the urate level remains high (>0.36 mmol/L) despite the patient being symptom free, there can be ongoing joint inflammation and hence joint damage and tophi formation.

4. ***Chronic tophaceous gout*** – tophi are firm white translucent nodules in connective tissue arising from the deposition of urate crystals. They can take at least 10 years after the initial attack to develop. As well as causing joint destruction, they are disfiguring and also cause physical hindrance. Tophi can become inflamed or infected and can exude tophaceous material.

DIAGNOSIS OF GOUT

The diagnosis of gout can be made according to the American College of Rheumatology (ACR)/Wallace criteria[1]:

A. The presence of characteristic urate crystals in the joint fluid,

B. A tophus proved to contain urate crystals by chemical means or polarized light microscopy (images are available in the online version of this article visit www.bpac.org.nz)

OR

C. Six of the following 12 clinical criteria

a. Maximum inflammation within the first day

b. More than one attack of acute arthritis

c. Monoarticular arthritis

d. Redness observed over joints

e. First metatarsophalangeal joint pain attack

f. Unilateral metatarsophalangeal joint attack

g. Unilateral tarsal joint attack

h. Suspected tophus

i. Hyperuricaemia

j. Asymmetric swelling within a joint on x-ray

k. Subcortical cysts with no erosions on x-ray

l. Negative bacterial culture of joint fluid

It is important to note that gout and sepsis can co-exist. The presence of urate crystals in synovial fluid does not exclude a diagnosis of sepsis.[2]

Although hyperuricaemia is a key risk factor for gout, it is not sufficient to make the diagnosis of gout; ***only 20% of patients with hyperuricaemia will develop gout***, and serum urate concentrations may be normal in patients during an acute gout flare.[3]

TREATMENT OF GOUT

Treatment of acute gout flares

Presenting symptom: Acute gout

- Treat acute attack with NSAIDs.
- Use corticosteroids when NSAIDs are contraindicated.

- Treat resistant cases with ***addition*** of low dose colchicine.
- Treat those at risk of NSAID side effects with colchicine ***alone***.

Evaluate and manage risk factors
(weight, alcohol, diuretics, dietary purines)

- ***NSAIDs:*** given at regular intervals until the severe pain abates, at which time the dose may be reduced (e.g. starting with naproxen 500 mg bd or diclofenac 75 mg bd). Always watch for renal impairment, heart failure and peptic ulceration. If patients are already taking low dose aspirin for cardiovascular risk reduction it should be continued.

- ***Oral corticosteroids:*** in view of the toxicity of colchicine, corticosteroids may be preferred to treat acute gout in patients in whom NSAIDs are contraindicated, provided sepsis has been excluded. The initial dose is 15–40 mg prednisone daily, gradually reduced over 10 days. Intra-articular corticosteroids are useful if monoarthritis is present to reduce risks of systemic therapy.

- ***Colchicine:*** can be a useful adjunct to NSAIDs in resistant cases, particularly when tophi are present, as monotherapy or to prevent flares when starting allopurinol.

- ***Allopurinol:*** If a patient has been taking allopurinol regularly at the time of developing an acute attack it should be continued at the same dose.

"Allopurinol should not be started at the time of the attack"

RISK FACTORS FOR GOUT

The key risk factors for gout are

- Hyperuricaemia
- Male sex
- Māori and Pacific ethnicity*
- Chronic renal impairment
- Hypertension
- Obesity
- Diuretic use**
- Coronary heart disease
- High intake of meat, seafood and alcohol (particularly beer)

*Māori patients with normal uric acid levels have been shown to have a reduced excretion of urate. This suggests an underlying renal mechanism.[4]

**Diuretic therapy is a risk factor for the development of hyperuricaemia and recurrent gout attacks. Diuretic therapy should be minimised and avoided wherever possible.

Adverse effects with Colchicine

Colchicine has a narrow therapeutic margin and considerable variation in absorption between individuals. Toxic effects include diarrhoea, nausea and vomiting, electrolyte imbalance, alopecia, haematological effects, pancreatitis, and failure of kidneys, liver or respiratory system. High doses can be fatal.

Colchicine dosing for acute gout

Due to recent concerns about toxicity, colchicine is no longer considered first line treatment for acute gout. In addition colchicine should be used at a lower dose than has been recommended in the past.

"…The recommended dose for colchicine in the treatment of acute gout is 1.0 mg stat, followed by 0.5 mg six hourly, up to a maximum dose of 2.5 mg per 24 hours…"

New Zealand Rheumatology Association (NZRA), endorsed by Medsafe.[5]

(full statement available at www.rheumatology.org.nz/colchicine.htm)

After the first 24 hours, the dose should be reduced to 0.5 mg one or two times daily, according to renal function. Prescribed in this way colchicine is safe and effective. The risk of diarrhoea and other toxic effects is minimised. Many patients report that one or two colchicine tablets taken within the first few hours of the onset of pain can avoid a major flare.

Adverse effects with Allopurinol

The most common adverse effect is a rash (1–2%), which may be more common in patients with renal impairment.[12] *Allopurinol hypersensitivity syndrome (AHS) is extremely rare but potentially fatal. It is characterised by fever, rash, eosinophilia, hepatitis and renal failure. Adverse effects can occur at any dose.*[13]

INDICATIONS FOR URIC ACID LOWERING THERAPY[6-8]

All patients with any one of the following should receive long-term uric acid lowering therapy:

- Recurrent gout attacks (≥2 attacks/year)
- Tophi
- Gouty arthropathy
- Radiographic damage
- Early onset, family history and serum uric acid >0.60 mmol/L

It should be noted that although effective treatment of gout can lead to regression of tophi, management is far more difficult once tophi develop, due to the high total body urate load.

"Early treatment of gout, before onset of tophi and erosive disease, is recommended"

HITTING THE TARGET IN GOUT: AIM FOR A SERUM URIC ACID CONCENTRATION OF <0.36 mmol/L

Several recent studies have emphasised the importance of excellent long-term control of serum uric acid in order to suppress gout attacks and achieve regression of tophi. These studies have identified a serum uric acid level of <0.36 mmol/L as the target required for dissolution of monosodium urate crystals within the joints and subcutaneous tissues.[9–11] This target has been endorsed in the recent European League Against Rheumatism (EULAR) guidelines for management of gout.[7]

Reduction of the serum uric acid level requires both pharmacological and non-pharmacological management. Allopurinol is the first choice urate-lowering drug unless there is a history of allopurinol allergy/ intolerance.

"Patients with gout should be encouraged to think of their uric acid level in the same way that patients with diabetes think of their HbA1c"

Allopurinol prescribing: a how-to guide

1. Wait for at least two weeks after an acute gout attack before starting allopurinol

2. *'Start low and go slow'*. Start with allopurinol 100 mg daily, and increase by 100 mg every two weeks until the serum uric acid level is <0.36 mmol/L. For most patients with normal renal function, a dose of 300 mg daily is needed to achieve this target. Patients with renal impairment may require less allopurinol to achieve this target. Sudden changes in the serum uric acid level are likely to precipitate gout attacks. Gradually increasing the dose of allopurinol is less likely to trigger a gout attack

3. Use prophylaxis against acute attacks. Prophylaxis with colchicine (0.5 mg daily to twice daily) or NSAIDs for the first three months of starting allopurinol (or until serum uric acid <0.36 mmol/L) should be prescribed to reduce the risk of gout attacks.[14]

4. Ensure the patient knows that the colchicine is for gout prevention and the dose should not be altered without medical advice if an acute episode occurs.

5. Monitor serum uric acid levels on a monthly basis while establishing allopurinol. Once serum uric acid is <0.36 mmol/L, monitor uric acid and renal function on a three-monthly basis.

6. Allopurinol should be continued as life-long therapy for management of gout, except in the case of allopurinol intolerance. Do not stop taking allopurinol during an acute attack of gout.

Other urate-lowering drugs

The uricosuric agent probenecid is an effective urate-lowering drug in patients with normal renal function and urate under-excretion. This agent is particularly useful in combination with allopurinol if there is persistent hyperuricaemia despite therapeutic doses of allopurinol, or in allopurinol intolerance.[15] A typical dose is 250 mg twice daily for two weeks, then 500 mg twice daily thereafter.

Probenecid is contraindicated in patients with a history of renal stones. Patients should be advised regarding the importance of high fluid intake while taking probenecid, around eight glasses of water per day.

LIFESTYLE INTERVENTIONS

Weight management is the key component in dietary management of gout. A 5% loss in body weight leads to a 10% reduction in serum uric acid level.[16,17] Diets very low in purines are generally unpalatable and poorly tolerated over time. Patients are more likely to accept advice to reduce purine-rich foods than to be told not to eat them at all (Table 1). Patients should be encouraged to eat regular meals and to drink plenty of water.

Table 1. Dietary advice for patients with gout

What to reduce in your diet	What to include in your diet
Red meat, shellfish, oily fish[18]	*Vitamin C[19]
Sugar and sugar-sweetened drinks[20]	Low fat dairy products[18,21]
**Alcohol, especially beer[22]	***Coffee[23,24]

**Studies suggest that Vitamin C might be beneficial in the prevention and management or gout and other urate-related diseases.[19]*

***Beer confers a larger risk than spirits. Moderate wine intake does not increase risk[22]*

****Refer to Bandolier article, page 33*

WHEN TO REFER TO A RHEUMATOLOGIST

Referral is appropriate when there is:

- Persistent hyperuricaemia or gout attacks despite maximum tolerated allopurinol treatment
- Doubt about the diagnosis
- Failure to achieve prompt resolution of acute attacks
- Development of progressive bone and joint damage on x-ray

URATE

Cam Kyle and Stephen Du Toit
Chemical Pathologists

About one third of body urate comes from the diet, two thirds from endogenous tissue catabolism. Underexcretion of urate by the kidneys is the cause of high serum levels in over 80% of adult patients. Insulin resistance (metabolic syndrome) is associated with increased urate resorption and higher serum urate levels.

About 20% of males have a serum urate above 0.42 mmol/L, but this has been chosen as the upper end of the male range because at that level urate becomes supersaturated in body fluids at 37°C, resulting in increased crystal deposition in tissues. Above this level the 5–year risk of gout rises fifty-fold from about 0.1% below 0.42 mmol/L to 5% above 0.54 mmol/L. Above 0.60 mmol/L the 5–year prevalence of gout is about 30%.

An upper limit of 0.36 mmol/L is used for women because their levels before menopause average 0.06 mmol/L lower than men. After menopause, levels in women approach those in men and the risk of gout increases, being similar to men over age 60.

Serum urate is the most important predisposing risk factor for gout, but is not used alone to make the diagnosis. Most patients with high urate levels do not develop gout and, conversely, serum urate may be normal, especially during acute attacks. Visual identification of crystals from joint fluid or tophi is the gold standard.

For patients with clinical gout on long-term treatment, a target urate level of 0.36 mmol/L has been recommended by some international bodies. The long-term risk of gout recurrence is much lower when levels are maintained below this threshold and it also favours the slow dissolution of chronic tophi, being well below the solubility constant of urate.

D-News, Diagnostic Medlab, August 2007 Available from: http://snipurl.com/1ptr8

CONSIDER CVD RISK AND METABOLIC SYNDROME FOR EVERY PATIENT WITH GOUT

There is increasing recognition that asymptomatic hyperuricaemia is an independent risk factor for development of CVD.[25] However, there is no current evidence that treatment of asymptomatic hyperuricaemia reduces the risk of subsequent CVD events.

Re-analysis of the Multiple Risk Factor Intervention Trial (MRFIT) has addressed the association of acute myocardial infarction (MI) in patients with gout. In this study, gout was associated with increased risk of acute MI (OR 1.3, $p < 0.001$), even after adjusting for BMI and metabolic syndrome.[26] In patients attending gout clinics in Auckland, 59% are at high risk of CVD events (>15% in the next five years) based on Framingham risk tables.[27]

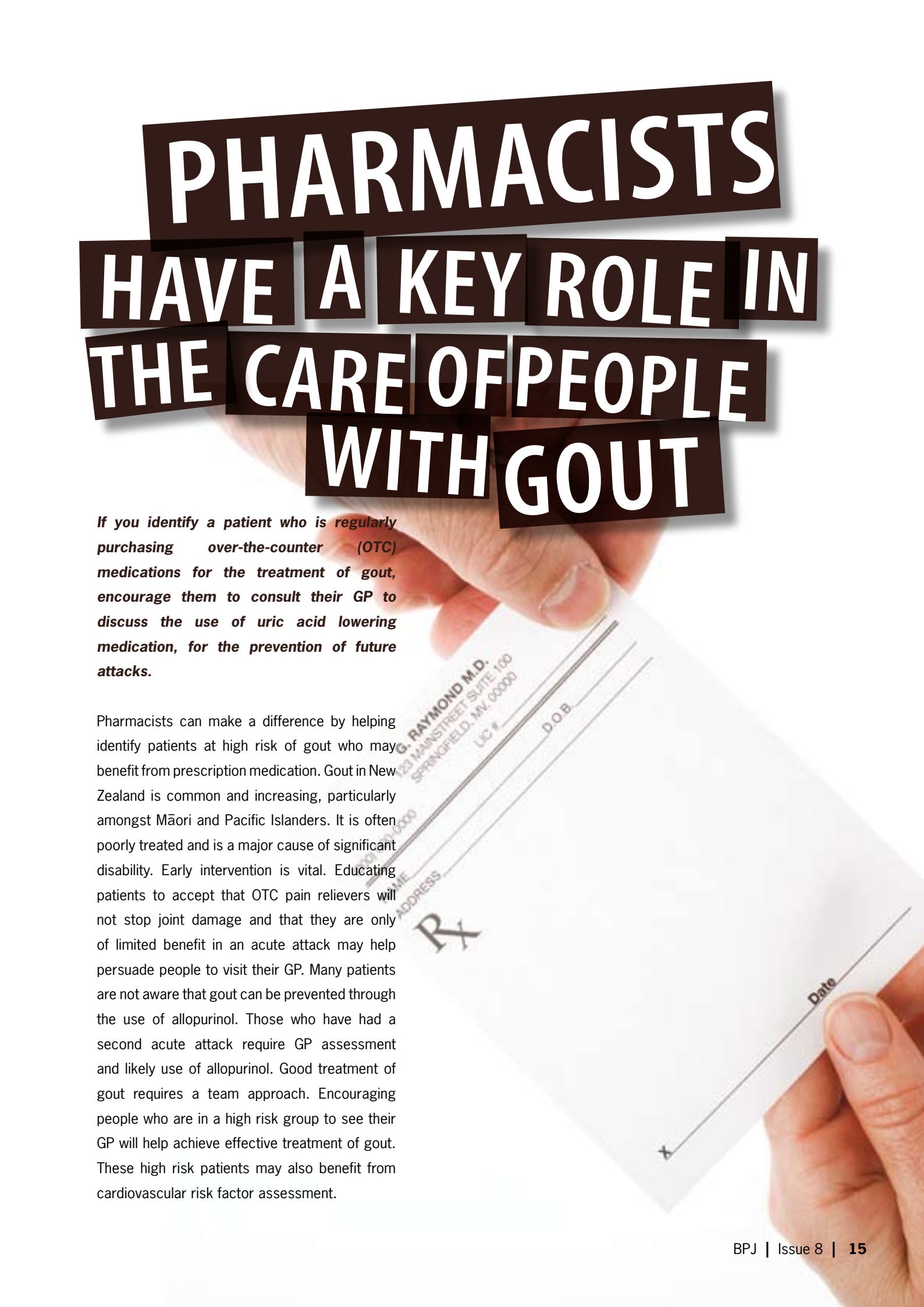
Recent analysis of the National Health and Nutrition Examination Survey (NHANES III) showed that gout is associated with increased risk of metabolic syndrome (OR 3.4, $p < 0.001$).[28] In patients attending gout clinics in Auckland, 87% have metabolic syndrome (using the revised Adult Treatment Panel (ATPIII) definition).[27]

"All patients with gout should have CVD risk assessment, and intensive management of modifiable risk factors"

PHARMACISTS HAVE A KEY ROLE IN THE CARE OF PEOPLE WITH GOUT

If you identify a patient who is regularly purchasing over-the-counter (OTC) medications for the treatment of gout, encourage them to consult their GP to discuss the use of uric acid lowering medication, for the prevention of future attacks.

Pharmacists can make a difference by helping identify patients at high risk of gout who may benefit from prescription medication. Gout in New Zealand is common and increasing, particularly amongst Māori and Pacific Islanders. It is often poorly treated and is a major cause of significant disability. Early intervention is vital. Educating patients to accept that OTC pain relievers will not stop joint damage and that they are only of limited benefit in an acute attack may help persuade people to visit their GP. Many patients are not aware that gout can be prevented through the use of allopurinol. Those who have had a second acute attack require GP assessment and likely use of allopurinol. Good treatment of gout requires a team approach. Encouraging people who are in a high risk group to see their GP will help achieve effective treatment of gout. These high risk patients may also benefit from cardiovascular risk factor assessment.



PREVALENCE AND IMPACT OF GOUT

MAORI AND PACIFIC PEOPLE OVER-REPRESENTED IN GOUT CLINICS

Gout is the most common form of inflammatory arthritis affecting men.[29] Gout is uncommon in pre-menopausal women. Most women with gout are post-menopausal and taking diuretics.

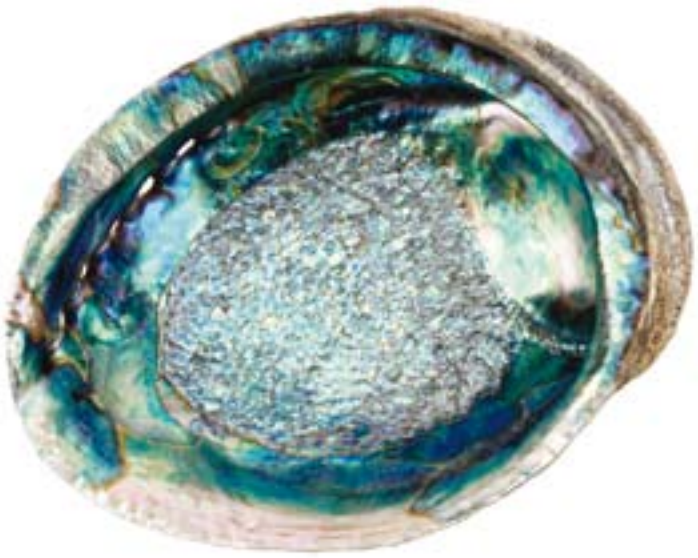
Gout is on the increase in New Zealand.[30] Recent data from primary care in Auckland shows that gout affects 14.9% Pacific men, 9.3% Māori men and 4.1% European men (Richard Hulme, East Tamaki Health Care, 2006). The same data has shown that gout is more frequently diagnosed than Type II diabetes in Māori and Pacific Island men.

Gout is now the most frequent cause for new patient referral to the rheumatology outpatient clinic in South Auckland, and accounts for more than 200 inpatient admissions to Middlemore Hospital each year.[31] Māori and Pacific patients with severe gout are over-represented within gout clinics in the Auckland area (Table 1).

Table 1. Percentage of Māori and Pacific Island people presenting to gout clinics in Counties Manukau DHB.[13]

	% DHB population	*% presenting to gout clinics*
Māori	17%	25.6%
Pacific Island	16%	46.0%

Māori and Pacific patients attending these rheumatology clinics have higher serum uric acid levels, more work disability and lower levels of musculoskeletal function than European patients (N. Dalbeth, unpublished data).



Why is gout such a problem in Māori and Pacific communities?

A study of gout patients in South Auckland has revealed some key issues (personal communication, Dr K Lindsay, CMDHB).

- There is minimal knowledge about gout and the medications used in treatment.
- Amongst the Pacific Island community in particular, there is a normalisation of gout, a stoicism and tolerance of the pain.
- Often knowledge of gout is based on jokes about over-indulgence, old age or unhelpful myths.
- These beliefs contribute to denial and result in missed opportunities for early diagnosis.
- Families take up the burden of caring for gout patients and these patients rarely present to general practice.
- Typically patients will use pain relief but not preventative medications, with a resulting increase in the number of joints involved, the size of tophi, the frequency of attacks and number of days off work. Without appropriate use of allopurinol, their gout is progressive and becomes chronic.

Genetic research into the causes of gout

Renal excretion of urate is controlled by a number of organic anion transporters and URAT1, the specific urate transporter that reabsorbs urate from the proximal renal tubules into the bloodstream. Genetic variants in URAT1 have been demonstrated to be a primary cause of gout in overseas populations. Researchers at the University of Otago, in collaboration with the New Zealand Rheumatology Research Network and Ngati Porou Hauora, are testing the URAT1 gene and other urate transport molecules for genetic variants causative of gout in patients of Māori and Pacific ancestry. Patients with variants in URAT1, that are a primary cause of gout, may benefit from treatment with uricosuric agents such as benzbromarone and probenecid which specifically inhibit the activity of URAT1. (J.Hollis-Moffatt,personal communication)

Further resources

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www.rheumatology.org.nz

www.arthritis.org.nz

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