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LAB INSIDER

THE GOUT GUIDE

I always find the etymology of the names for medical conditions rather interesting and in this newsletter we're discussing gout. The word originates from the Latin *gutta* although the condition was well described by Egyptian and Greek physicians who considered it a disease caused by drops of fluid or evil humours that accumulated in the joints and formed the chalky lumps of crystal we now call tophi.

The English word 'gout' traces back to *gutta* (drop) via the French *goutte* but it took an odd turn at some point. Adopting the French word for diseases was common, however, in doing so English physicians either got the spelling wrong or just shortened the French word *goutte* to gout, which is actually a misnomer (*gout* in French means taste). Despite the oversight the name stuck.

Before taking a closer look at gout (caused by high uric acid), let's get the causes of low uric acid out the way because they are sometimes a curious finding and a source of confusion.

Dr Pierre Durand

DIABETES, URIC ACID & GOUT

The textbooks list the causes of a low uric acid (UA) level as a range of genetic conditions, kidney diseases like Fanconi syndrome, medications and dietary preferences like veganism. One condition that is sometimes left out is uncontrolled type 1 diabetes mellitus and it comes as a surprise when the level is unexpectedly found to be very low. The pathological explanation is complex.

UA levels are typically low in T1DM (and normal or high in T2DM) because glucose competes with UA reabsorption in renal tubules, although there are also factors like dehydration and ketosis which acidify the urine and decrease reabsorption. This may also lead one to expect renal lithiasis to be more common in T1DM but in fact the opposite is true because in T2DM insulin resistance affects ammonia secretion (and to a lesser degree active UA secretion).

The result is that in T2DM the urine acidifies which promotes renal lithiasis of mixed composition. (In T1DM, glycosuria is the main driver of lithiasis and the stones comprise pure UA.)

Gout, as you expect due to the differences in UA levels, is also much more common in T2DM. This is not only because of the elevated UA in urine in T1DM, but there is also and overlap with metabolic syndrome in T2DM with factors like obesity, renal compromise, diet etc. all contributing to elevated uric acid.

However, as I indicated earlier, the pathogenesis of gout and renal lithiasis in DM is multifactorial with glycosuria, acidosis, dehydration, uric acid levels and metabolic syndrome all playing a part.

URIC ACID METABOLISM & HYPERURICAEMIA

In humans, the overwhelming source of uric acid is the degradation of purines (guanine and adenine). Through a series of biochemical steps the final product is uric acid, which is then filtered by the renal glomeruli and actively excreted by the proximal tubules (75%), and actively excreted or passively diffused into the intestines (25%).

Because most (90%) of the UA in the urine is reabsorbed (UA in the gut is not reabsorbed), there is tendency to erroneously refer to a uric acid cycle in humans. There is such a cycle (discovered by Krebs who actually has four different eponymous metabolic cycles), but not in humans. A true uric acid cycle is only found in birds because they are able to use reverse peristalsis to move the uric acid from the cloacae into the bowel where microbes convert UA into amino acids and purines.

These macromolecules are then reabsorbed and the purines either re-incorporated into nucleic acids or broken down again into uric acid. In humans, the metabolism of purines ends with UA because we don't have a functional uricase gene. Other mammals like our pet dogs and cats do have a functional uricase which breaks down UA into allantoin, a harmless compound that is easily excreted. Curiously birds also lack a uricase, but their kidneys are so efficient that they excrete uric acid easily without reabsorbing it and the UA precipitates into the white pasty substance you will have noticed in their droppings.

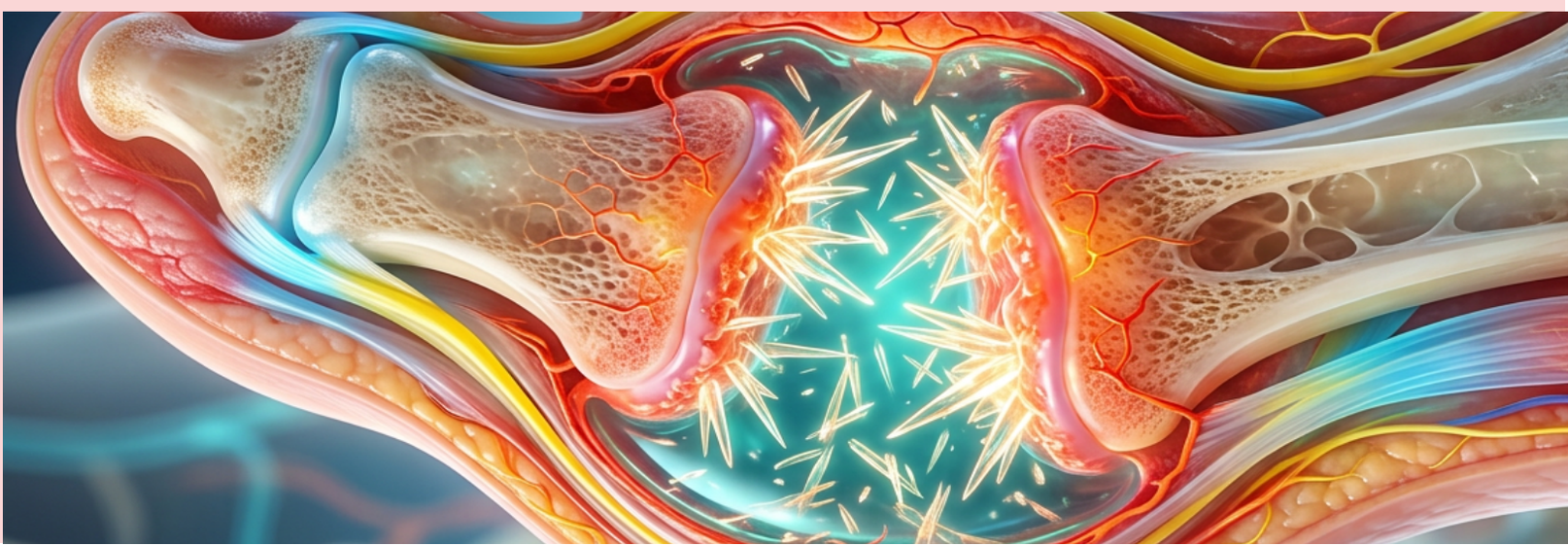
SOURCES OF PURINE IN HUMANS

Most of the purines in humans are endogenous in origin (~85%). They are synthesized de novo from amino acids, carbon dioxide and phosphorylated ribose. The intermediate metabolites can also be recycled via a salvage pathway before forming the end product of UA. Conditions with high cell turnover lead to increased purine breakdown, which is why gout is frequent in some cancers.

Exogenous dietary sources of purines come from animal protein, alcohol and some sugars (predominantly fructose in sugary drinks), which is why gout used to be called a rich man's disease. But of course, alcohol is often more prevalent in poorer communities (first nations in North America, Australia, New Zealand) and marginalised peoples in other colonised countries so the moniker of rich man's disease isn't that appropriate anymore, if indeed it ever was.

For completeness, the genetic conditions that cause gout are most commonly those with mutations in cellular transporters. For example, some conditions inhibit UA secretion into the gut, while others increase renal reabsorption. There is also a host of polymorphisms in the transporters, which is why clinical gout is so variable.

There are other genetic conditions that cause an over-production of purines (e.g., Lesch-Nyhan Syndrome) or kidney diseases (e.g., Juvenile Hyperuricaemic Nephropathy), which leads to gout as well as the many other more serious problems



ACUTE AND CHRONIC GOUT SYMPTOMATOLOGY

Gout is very, very painful. I remember my dear Uncle Jim who was a poster child for gout. He was a farmer in central Africa and without access to medical help (or perhaps he refused it) he showed all the signs of chronic gout and intermittent acute flareups. Chronic gout is illustrated primarily by arthritis in multiple joints, tophi, and renal stones and, of course, pain. Uncle Jim had more tophi that I have ever seen—he was essentially one large tophus. They even formed on the pinnae of his ears and as children we loved when he visited because they often broke through the skin and he pulled them out and gave them to us as Christmas presents.

The acute flareups can be sudden and affect any joint, although it is often taught that the most vulnerable joint is the first metatarsal. Symptoms include inflammation with redness, swelling, and immobility. And pain. Oh boy, the pain. As kids, we hadn't yet learnt an appropriate empathy and instead saw the funny side of this in Uncle Jim, primarily because he didn't suffer in silence. I still haven't figured out what some of the words meant, but having my parents cringe at his language was always a source of amusement.

Gout crystals are visually impressive (Figure 1), but it's not just a question of aesthetics. Consider for example the differentiation between uric acid / urate (gout) crystals and calcium pyrophosphate (pseudogout) crystals. Distinguishing the two microscopically is important because it is an indicator of urine acidity and thus affects treatment. The difference can be identified by their birefringence (figure 1). In gout the crystals demonstrate negative birefringence (yellow and blue depending on angles, left panel) and in pseudogout the crystals are blue (positive birefringence, right panel).



PATHOLOGY INVESTIGATIONS

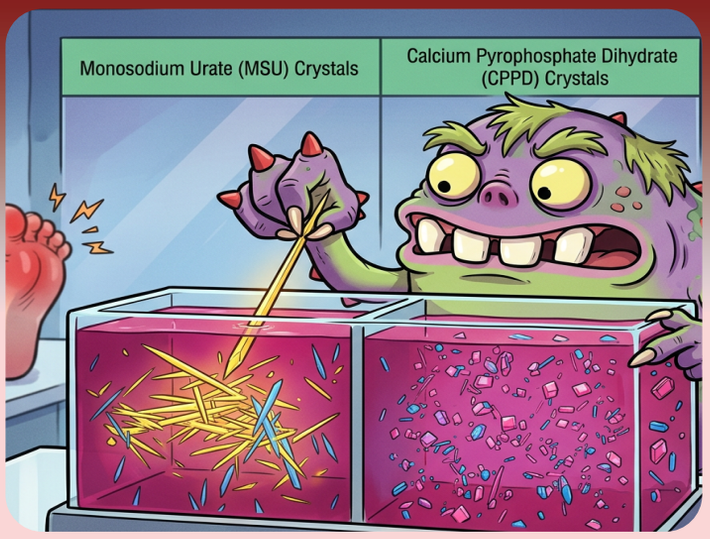
When gout is suspected, there is a panel of relevant investigations. In many cases, physicians simply test the uric acid and this can be appropriate if the clinical history warrants it. However, for a first-time presentation, if there is any doubt the following are recommended (Table1).

Table 1: Investigations in gout and other causes of arthritis.
The investigations listed are for cases where a clinical diagnosis requires further guidance. For example, in cases of arthritis of unknown cause a full arthritis workup may be necessary.

clientservices@togalab.co.za

011 663 6300

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DISCIPLINE	INVESTIGATIONS
Radiology	X-rays, ultrasound or CT scanning as appropriate
Microscopy	Joint fluid and urine
Serum/Whole Blood	FBC, U and E, Uric acid, LFTs, TFTs, ESR, CRP, auto-immune markers and general arthritis work-up.

CONCLUDING REMARKS

Gouty arthritis is very common in all communities and treatments are typically effective. However, assuming gout when the presentation is not typical is usually inappropriate and can lead to adverse outcomes. Frequently, for various reasons like cost and time, further investigations are not done, and the disease is treated empirically. But unless it is a cut and dried case, it is strongly advised to pin down the condition and screen for possible complications.

References available on request.

