URIC ACID, GOUT AND PURINE METABOLISM

BY

DR. OMAR J KATWAN

CLINICAL BIOCHEMIST

Serum urate

A high serum urate, called hyperuricaemia, is a result of excessive formation, reduced excretion or a combination of both (Figure 19.1). Other factors that influence levels are as follows:

- *Sex:* Serum levels are higher in males (0.12– 0.42 mmol/L) than in females (0.12–0.36 mmol/L).
- *Obesity:* Levels tend to be higher in the obese.
- *Social class:* The more affluent social classes tend to have a higher serum urate.
- *Diet:* Serum urate rises in individuals taking a high-protein diet (especially meat or seafood). High alcohol consumption and fructose-containing beverages are also associated with raised serum urate. Dairy foods and coffee drinking appear to lower urate when examined in epidemiological studies.
- *Genetic factors*.

Hyperuricaemia

In addition to the deposition of sodium monourate crystals in affected joints (see Chapter 19: Gout) uric acid calculi in the kidneys may also form due to hyperuricaemia, and the lower pH values possible in urine can predispose to this problem. As serum urate levels rise, the risk of precipitation of sodium urate increases, although the relationship between the presence and severity of hyperuricaemia and the development of arthritis or renal calculi is more complex than simple considerations of solubility might suggest.

1- Dietary factors

- *High-purine diets:*
- *Alcohol excess:*
- *Fructose-containing beverages:*

2- Endogenous overproduction of urate
3- Defective elimination of urate

Gout

Hyperuricaemia is associated with *gout*, a condition characterised by recurrent attacks of monoarticular arthritis. Typically this involves the first metatarsophalangeal joint but the ankle, knee or other joints may be involved. Articular gout may be preceded by an asymptomatic phase of hyperuricaemia, followed by acute attacks with symptom-free periods and eventually leading to chronic, gouty arthritis. Patients with chronic, primary gout (see Case 1) often show deposition of urate as tophi in soft tissues. Some also develop renal stones, mainly composed of uric acid, increasing the risk of renal dysfunction. The incidence of renal stones varies widely, largely depending on the presence of other contributory factors such as dehydration or a low urinary pH. There appears to be a high prevalence of metabolic syndrome with increased cardiovascular risk, and an association of gout with hypertension is increasingly recognised. Cardiovascular disease, in particular, is an important cause of morbidity and mortality in patients with gout. The condition is more prevalent in men, rises with age and, in women, typically occurs after the menopause.

Case Study 1

A 48-year-old manager was admitted with severe colicky pain in his lower left lumbar region and an associated history of haematuria. He was overweight with a blood pressure of 165/105. Serum lipids on the admission sample showed triglyceride levels of 5.2mmol/L, a total cholesterol of 7.2mmol/L and an HDL cholesterol of 0.8mmol/L. Serum calcium was normal but the urate was 0.75mmol/L. Further questioning revealed an episode of severe pain in the first metatarsophalangeal joint of his left foot while holidaying in Spain. This was treated while abroad and resolved after a few days but he could not recollect what treatment had been given. What is the likely cause of this man's condition?

Comment: The clinical history here, together with the high serum urate level, all point towards the diagnosis of primary gout. The first metatarsophalangeal joint is the most common to be involved in first attacks of gout. The acute joint pain itself coincides with the time the patient was on holiday and possibly overindulging in alcohol and rich foods that may well have precipitated the initial episode. The high serum urate is likely to be longstanding and has led to the formation of renal stones. A history of severe lumbar pain, colicky in nature and associated with haematuria, is classical for renal colic. Where possible, examination of any stones passed or removed should be undertaken to confirm that these are composed of uric acid. There is a known association of gout with hyperlipidaemia, particularly a raised triglyceride. Associations with hypertension, obesity and IGT are also described.

Hypouricaemia

Low serum urate may arise as follows (Table):

• Dilutional states such as pregnancy.

• Decreased production. This can be found in severe liver disease. Another example is the condition called xanthinuria arising from an inherited deficiency of the enzyme xanthine oxidase (which normally converts xanthine to urate). Xanthine crystals can form in the urinary tract.

• Increased excretion. This is usually in association with defective proximal tubular reabsorption (Fanconi syndrome).

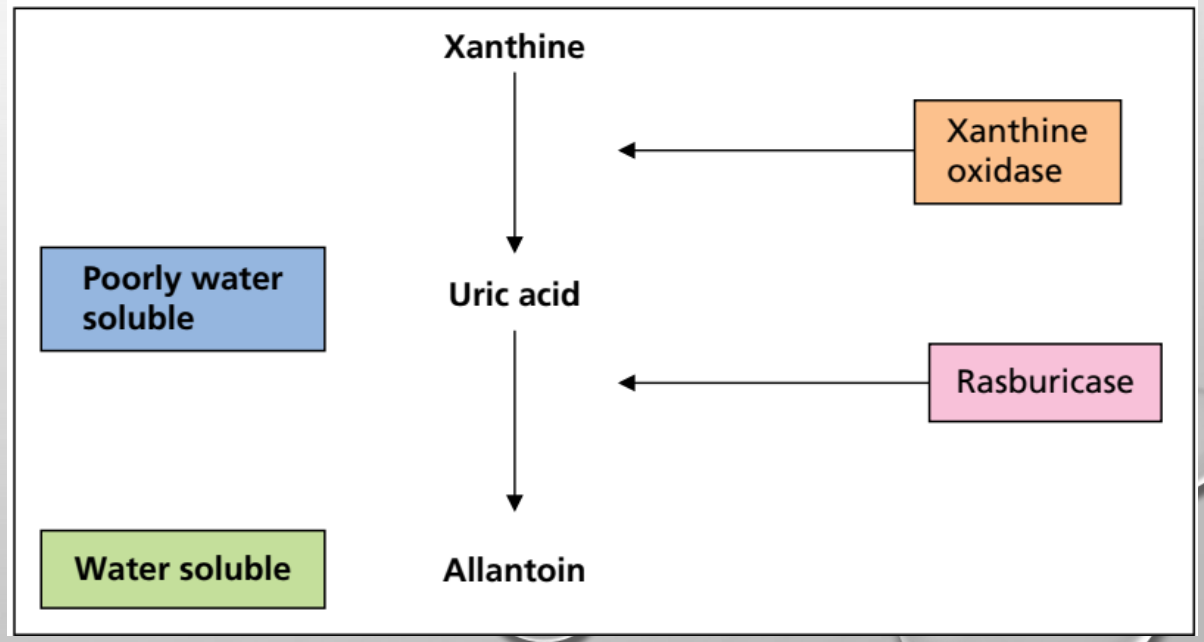
• Rasburicase (Figure). This is a genetically engineered enzyme that is a urate oxidase. It converts uric acid to the water-soluble allantoin. It is especially helpful in preventing the renal and other complications of excessive urate formation in the tumour lysis syndrome (massive cell lysis such as is found during treatment of haematological malignancies). It has a short half-life but can effectively reduce serum urate to very low levels. Modifications of rasburicase to increase its half-life are starting to find a place in the treatment of gout.

Table 19.3 Causes of a low serum urate.

Plasma dilution
- SIADH (Chapter 2: Hyponatraemia with normal ECF volume)
- Pregnancy

Decreased formation
- Xanthine oxidase deficiency
- Severe liver disease
- Rasburicase treatment

Increased excretion
- Uricosuric drugs (e.g. allopurinol)
- Fanconi syndrome



Case study 2

While authorising clinical results prior to release to the wards, the clinical biochemist on duty was surprised to find a serum urate level that was extremely low (undetectable on the laboratory analyser). Initially, she felt that this must have been an analytical error and asked for the result to be repeated. Again, the serum urate was undetectable. She rang up the haematology ward to discuss this result with the Specialist Registrar. Can you suggest a likely explanation for this finding?

Comment:

It turned out that the patient had an acute lymphoblastic leukaemia which was being actively treated. In anticipation of possible problems arising from the excessive formation of urate (as a consequence of massive cell lysis), the patient was on treatment with rasburicase. This is a genetically engineered urate oxidase which converts uric acid to the water-soluble allantoin. It is so effective as to reduce the serum urate to virtually undetectable levels, hence the laboratory finding which was a correct analytical result!

Thank you for your attention