Disorder of protein, Uric acid, gout and purine metabolism

Purine metabolism and uric acid

Purines are simple, cyclic organic molecules that are essential constituents of the nucleic acids, both DNA and RNA. The purine bases adenine and guanine comprise the 'A' and 'G' of the DNA code. When a ribose sugar moiety is linked to the purine base a nucleoside is formed (e.g. adenosine, made up of the purine adenine linked to ribose). The addition of a phosphate group to the ribose ring generates the corresponding nucleotide (e.g. adenosine 5-monophosphate, AMP). As such the purines are essential constituents of metabolically important compounds such as ATP. Uric acid is the end-product of breakdown of the purine bases. It emphasizes that the source of the purines can be from the three routes of diet, nucleic acid breakdown or de novo purine synthesis. The liver is the main source of urate and, once formed, urate is predominantly excreted via the kidneys. The clinical importance of purines rests largely on the disorder termed gout, an inflammatory arthritis resulting from uric acid deposition in the joints. An increase in serum uric acid (as the anion, urate, at physiological pH) is the strongest risk factor for gout although gout may occur when serum urate levels are within the normal range. In man, urate is the end-product of purine metabolism such that urate accumulation may arise from:

• increased dietary purine intake or dietary factors affecting urate production;

• increased formation (either increased nucleic acid breakdown or increased de novo synthesis of purines);

• decreased renal excretion

Hyperuricaemia

In addition to the deposition of sodium monourate crystals in affected joints 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.

Dietary factors

• **High-purine diets**: A high meat diet or one rich in seafood increases the purine load.

• **Alcohol excess**: Nutritional surveys have established a strong link between hyperuricaemia and alcohol intake.

• **Fructose-containing beverages**.

Endogenous overproduction of urate

A number of mechanisms are possible. For example:

• Unspecified overactivity of the pathways of nucleotide metabolism, as opposed to nucleic acid synthesis, leading to urate formation (‘endogenous overproduction’).

• Decreased activity of the ‘salvage’ pathway so that purine bases are metabolised to urate rather than reincorporated into nucleotides and nucleic acids.

• Increased nucleic acid breakdown when cell turnover or destruction is increased.

Defective Elimination of Urate

Renal excretion of urate is a complex process. Except for a small fraction bound to plasma proteins, urate is completely filtered at the glomerulus; this is then mostly reabsorbed in the proximal tubule. In the distal tubule, there is both active secretion and post secretory reabsorption at a more distal site. These processes can all be affected by disease or drugs:

• **GFR**: When the GFR becomes reduced for any reason urate retention occurs.

• **Tubular reabsorption**: Around 90% of the filtered urate load is reabsorbed in the proximal nephron via specific anion transporters. The specific transport called URAT1 is a target for drugs such as probenecid that inhibit its activity and increase the excretion of urate.

• **Distal tubular secretion**: Urate excretion also depends upon distal tubular secretion. This process is competed for by other organic acid anions such as lactate and 3-hydroxybutyrate. Any condition that gives rise to lactic acidosis or ketosis tends to be associated with hyperuricaemia.

Gout

Hyperuricaemia is linked to gout, which causes recurrent attacks of painful monoarticular arthritis, commonly affecting the first metatarsophalangeal joint. Gout usually progresses from an asymptomatic phase to acute attacks and may later become chronic with tophi formation.

Urate deposition can also cause kidney stones, increasing the risk of renal dysfunction, especially with dehydration or low urine pH. Although common in older men and post-menopausal women, many people with high serum urate never develop gout, and acute attacks may occur even with normal urate levels.

• **Primary gout**, by definition, occurs in the absence of acquired or monogenetic conditions although there is no doubt that genetic factors contribute, with about 60% of variability in serum urate genetically determined.

The present evidence is that differences in urate excretion rates contribute principally to urate levels, overproduction being a less important factor. The association with hyper lipidaemia, ischaemic heart disease and metabolic syndrome may also reflect a familial component,

Diagnosis of gout is usually clinical, based on typical joint involvement, previous similar attacks, response to colchicine, and raised serum urate after excluding secondary causes. However, high serum urate supports but does not confirm gout, and up to one-third of patients may have normal levels during an acute attack. Acute gout occurs when urate crystals enter the joint and are taken up by immune cells. There are rare forms of gout that arise from clearly defined and inherited metabolic enzyme defects which increase uric acid formation. It is convenient to categorise these enzymatic defects as secondary gout to distinguish them from the common primary gout.

• **Secondary gout** describes the condition in association with other disorders that secondarily increase urate formation (e.g. increased cell death in myeloproliferative disorder) or decrease excretion (e.g. renal failure). The group also includes the rare metabolic causes of overproduction.

Hypouricaemia : Low serum urate may arise as follows

• Dilutional states such as SIADH (Syndrome of inappropriate antidiuretic hormone) or pregnancy.

• Decreased production. This can be found in severe liver disease.

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