How to Cite:
Shebi, S., & Chokkattu, J. J. (2022). An updated review on gout. *International Journal of Health Sciences*, *6*(S2), 11950–11957. https://doi.org/10.53730/ijhs.v6nS2.8230

An updated review on gout

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***Abstract*---**First identified by the Egyptians in 2640 BC, podagra (acute gout occurring in the first metatarsophalangeal joint) was later recognized by Hippocrates in the fifth century BC, who referred to it as 'the unwalkable disease'. The term is derived from the Latin word gutta (or 'drop'), and referred to the prevailing medieval belief that an excess of one of the four 'humors' - which in equilibrium were thought to maintain health - would, under certain circumstances, 'drop' or flow into a joint, causing pain and inflammation. Throughout history, gout has been associated with rich foods and excessive alcohol consumption. Because it is clearly associated with a lifestyle that, atleast in the past, could only be afforded by the affluent, gout has been referred to as the 'disease of kings'. Although there is evidence that colchicine, an alkaloid derived from the autumn crocus (Colchicum autumnale), was used as a powerful purgative in ancient Greece more than 2000 years ago, its first use as a selective and specific treatment for gout is attributed to the Byzantine Christian physician Alexander of Tralles in the sixth century AD.

***Keywords*---**updated review, gout, staple culture.

Introduction

The earliest definite evidence of gout was found in 1910, when the mummy of a man was excavated near a temple at Philae, in Upper Egypt(1).Examination revealed that he had suffered from an advanced stage of the disease. Since gout was already well-known when the mummy was a living man, he almost certainly got medical treatment. The Egyptians had already identified gout as a distinct disorder by 2640 B.C, and references to it are found in the earliest medical texts. Both the Ebers and Edwin Smith Papyri describe a condition that is clearly gout(2). They were written

about 1552 BC but contain information taken from texts a thousand years earlier, and ascribed to Imhotep, a kind of ancient world Leonardo da Vinci, and the great overarching figure of Egyptian medicine(3). Gouty arthritis was among the earliest diseases to be recognized as a clinical entity. First identified by the Egyptians in 2640 BC (4), podagra (acute gout occurring in the first metatarsophalangeal joint) was later recognized by Hippocrates in the fifth century BC, who referred to it as 'the unwalkable disease'. Throughout history gout has been associated with rich foods and excessive alcohol consumption. Because it is clearly associated with a lifestyle that, at least in the past, could only be afforded by the affluent, gout has been referred to as the disease of kings'. In some eras gout was perceived as socially desirable because of its prevalence among the politically and socially powerful. In his classic monograph on the history of gout (5). In recent decades, however, the diet and lifestyle that predispose individuals to hyperuricemia and gout have become increasingly common. The role of excess dietary purines (derived from meat,seafood, and beer) in the development of gout is illustrated by the disparity between the incidence of gout in Asia and Europe. Traditional Asian diets, based on rice and vegetables, are low in dietary purines, and gout has been relatively rare in these cultures. In contrast, European and American diets, which are high in meat and certain seafoods, are associated with hyperuricemia and gout (6). Because of its genetic distribution gout also developed a powerful moralistic aspect(7). Gout was such a staple of the culture that it was not just bemoaned, or used for a laugh --the elderly man lecherously staring at a comely maid, as he is consigned to his chair with gout -- it became a literary device(8). Gout, because it was a disease of rich men who shaped the world, and could get things done, was also a font of domestic technological development which only such men could afford(9). "Gout is over whelmingly a disease of adult Caucasian males," Dr. Meyerhoff points out(7).

Gout- causes

It is due to accumulation of urate crystals in the synovial fluid resulting in inflammation leading to acute arthritis. At 30 degree Celsius, the solubility of uric acid is lowered to 4.5mg/dL Therefore uric acid is deposited in cooler areas of the body to cause tophi. Thus tophi are seen in distal joints of foot. Increased excretion of uric acid may cause deposition of uric acid crystals in the urinary tract leading to calculi or stone formation with renal damage. The main metabolic abnormality in patients with gout is an increased cellular pool of PRPP, the substance for the rate limiting step of de novo synthesis of purine nucleotides. The resultant increase in the activity of amino transferase leads to excess production of nucleotides resulting in hyperuricemia(10). Compared with women, men have a four- to nine-fold increased risk of developing gout. Women often do not develop gout until they reach menopause, when the uricosuric action of estrogens is lost. As a rule, in Germany gout is treated primarily by primary care physicians and internists. Patients with persistent disease, those with an atypical course with polyarticular gout or joint destruction, or those whose cases are complicated by progressive kidney failure or allopurinol intolerance are treated by rheumatologists or nephrologists (11). Acute gout is a common cause of arthritis, affecting approximately 1% of the adult population, and epidemiological evidence suggests that its prevalence is increasing.Current treatments during an acute attack include nonsteroidal anti- flammatory drugs (NSAIDs), colchicine and

corticosteroids. Although these agents are generally effective, they also present significant risks in patients who have pre-existing renal, cardiovascular and gastrointestinal diseases (12). Concomitant slow and insidious deposition of uric acid in the tissues, which in some instantaneous progresses to disabling and deforming chronic gouty arthritis. Chronic is also known as tophaceous gout. Urate-lowering therapy (ULT) should be used to initially reduce and finally eliminate tissue deposits in patients with chronic gout(13). It has been suggested that ULT should be used to reduce serum uric acid levels to less than the threshold for saturation of uric acid in body fluids. Nevertheless, some experts contend that, to prevent further gouty episodes and to enhance mobilization of urate deposits, serum urate should be lowered to <6.0 mg/dl in patients with chronic gout and <5.0 mg/dl in patients with tophaceous gout (14). However, there is no consensus as to the Optimal level of serum urate during ULT to reduce deposits in gouty patients. It is uncertain if there is a relationship between serum uric acid levels during ULT and the velocity of reduction of urate deposition in tissue (15).

Uric Acid as a Factor in The Causation of Gout

Anton van Leeuwenhoek (1632-1723), one of the pioneers of microscopy, was the first to describe the appearance of the crystals from a gouty tophus, although their chemical composition was unknown at that time. He wrote in 1679(11). In 1776 the chemical identity of uric acid was first established as a constituent of a renal calculus by the Swedish chemist Scheele and the English chemist Woolaston demonstrated urate in a tophus from his own ear in 1797 (16). Fifty years later, Sir Alfred Baring Garrod described his famous "thread test', a semiquantitative method for the measurement of uric acid in the serum or urine; it was the first clinical chemical test ever undertaken (17). In his remarkable volume The Nature and Treatment of Gout and Rheumatic Gout (1859), Garrod stated that, "the deposited urate of soda may be looked upon as the cause, and not the effect, of the gouty inflammation" Experimental support for this hypothesis later came from Freudweiler's demonstration that acute gouty arthritis could be precipitated by the intra-articular injection of microcrystals of sodium urate (18) and from the work of His, which demonstrated the formation of tophi following subcutaneous injection of urate crystals. These experiments were over-looked for more than half a century until the publication of a seminal paper by McCarty and Hollander (18), which showed that crystals from the synovial fluid of patients with gout were composed of monosodium rate. Their classic report described the use of compensated polarized light microscopy to examine joint fluid for crystals, and this technique was subsequently used to identify calcium pyrophosphate dehydrate crystals in synovial fluid from the joints of patients with chondrocalcinosis and 'pseudogout' (15)

Types of Gout

- Primary gout
- Secondary gout
- Pseudo gout

Primary Gout

About 10% of cases of primary gout are idiopathic. Primary gout may show a familial incidence. Incidence of primary gouts is about 1:500 in total population. It is an inborn error of metabolism due to over production of uric acid. This is mostly related to increased synthesis of purine nucleotides. The metabolic defects associated with primary gout are

- PRPP synthetase:
  Uncontrolled PPP synthesise may lead to the increased production of purines
- PRPP glutamyl amidotransferase:
  Lack of feed back regulation of this enzyme leads to the overproduction of purines
- HGPRT deficiency:
  The defect in the enzyme is associated with the increased production of purine nucleotides. The defect in the salvage enzyme "leads to decreased levels of IMP and GMP causing impairment in the tightly controlled feed back regulation.
- Glucose 6 phosphatase deficiency:
  In type I glycogen storage disease (vongierkes) glucose 6 phosphate cannot be converted to glucose due to the deficiency of the enzyme glucose 6 phosphatase. this leads to an increased utilisation of glucose by HMP shunt resulting in elevated levels of ribose 5 phosphate and PPP and ultimately purine overproduction.
- Elevation of glutathione reductase:
  Elevated enzyme causes a increased generation of NADP which is utilised by HMP shunt thus leading to increased synthesis of purines (19)

Secondary Gout

Secondary hyperuricemia is due to various diseases causing increased synthesis or decreased excretion of uric acid. It may be due to enhanced turnover rate of nuclei acids as seen in:

For Increased Production of Uric Acid

- Rapidly growing malignant tissues, eg. leukaemias, lymphomas, polycythemia.
- Hyperuricemia is also seen in cancers patients on radio therapy or chemotherapy
- (tumour lysis syndrome) due to increased cellular turnover. Hence these patients are given allopurinol also, to decrease uric acid levels. Rasburicase is also found to be effective in these cases.
- Increased tissue damage due to trauma and raised rate of catabolism as in starvation.

For Reduced Excreted Rate

- Renal failure
- Treatment with thiazide diuretics which inhibit tubular secretion of uric acid.
- Lactic acidosis and Keto acidosis due to interference with tubular secretion(20)

Clinical Features

Urate is the end product of purine metabolism. Important steps in this are the degradation of xanthine and hypoxanthine by the enzyme xanthine oxidase. Urate is excreted primarily via the kidneys. In recent years important urate transport proteins such as the human URAT1 transporter (hURAT1) and the fructose transporter SCL2A9 have been characterized (21). Polymorphisms in the corresponding genes lead to a disturbance in the function of the transporters, with reduced renal urate excretion and consequent accumulation of urate, and are often associated with gout(22). The transport function is also affected by various drugs: for example, low-dose aspirin treatment and diuretics reduce urate excretion by inhibiting hURATI (23). In practice, these conditions in which the excretion of urate is reduced can be distinguished from other, rarer causes of hyperuricemia in which the production of urate is increased, e.g., in hematological diseases with increased cell turnover. The usual triggers of gout attacks are a sudden rise in serum urate, e.g., after excessive eating and alcohol intake. A rapid drop in serum urate, as for example at the start of urate-lowering therapy, can also trigger an attack of gout. In this case the release of urate from the margins of crystal deposits as a result of the concentration gradient between serum and tissue seems to stimulate an immune response (12). The typical first manifestation of gout is an acute episode of monoarticular arthritis at the metatarsophalangeal joint of the large toe (podagra) that is very painful, starts at night, lasts around a week, and in many cases is self-limiting (20).The deposition of urate crystals in various tissues such as joints, connective tissue, and kidneys explains the chronic character of the gout. Almost 90% of patients who have suffered an attack of gout experience repeat episodes during the following 5 years. In the course of the disease atypical manifestations may be seen: other joints may be affected, and oligoarticular or polyarticular arthritis may develop. The differential diagnosis includes other crystal-induced forms of arthritis such as pseudogout /chondrocalcinosis with deposition of calcium pyrophosphate dihydrate crystals, and oxalosis (21).

Diagnosing Gout

A suspected diagnosis of gout may safely be made on the basis of an episode of excessive eating and/or drinking (of alcohol) in the recent history- e.g., a barbecue- when the large toe shows the typical signs of a gout attack and the serum concentration of urate is raised. It is quite common for the serum urate level to be normal or low during an attack, so the best time to measure it is 2 to 3 weeks after an attack (evidence level [EL] IV) (23). If the manifestation is atypical and serum urate normal, joint puncture to demonstrate the presence of crystals is highly desirable (ELIIb; the differential diagnosis in such a case includes septic

arthritis (21). The important thing here is to examine the untreated crystals (urate crystals dissolve in formalin) under a polarization microscope. The crystals appear as birefringent intra-and extracellular needles 10 to 20 um in length. Once gout has been diagnosed, the possible causes need to be identified. Since, given the appropriate genetic predisposition, it is possible that, in addition to the increased urate (often promoted by diet), cell turnover may in rare cases be increased due to the presence of occult neoplastic disease (e.g., leukemia or plasmacytosis), cell count, differential cell count, and erythrocyte sedimentation rate should be carried out, together with determination of lactate dehydrogenase and possibly serum albumin electrophoresis (EL IV) (24).If no explanation for the gout attack is found, especially in younger patients with a family history of gout, then owing to the frequent association with impaired renal function, serum creatinine should be determined, as should 12- or 24-hour urinary clearance of creatinine and urate, and a urinary pH strip test should be performed (EL IIb) (12). Since patients with gout have an up to 2.5-times increased risk of developing urate stones, leading to urate nephropathy, the kidneys should be examined by ultrasound to rule out the presence of stones. Because of the frequent association with other metabolic and endocrine diseases- over 50% of patients have a metabolic syndrome- the guidelines for risk stratification recommend determination of fasting blood sugar, and possibly of HbA1c, fasting blood lipids/cholesterol, and thyroid parameters (EL Ila to Ilb) (19).

Treatment

The first therapeutic goal is acute treatment of the gout attack with rapid alleviation of pain and inhibition of the inflammation. A longer-term goal is to prevent further attacks, eliminate tophi, and prevent joint destruction, by consistently reducing the level of urate (5). It is postulated that gout is "curable" if existing deposits of urate crystals can be successfully removed and the formation of new precipitates prevented(16). To achieve this, according to international recommendations, serum urate levels in patients with recurring attacks of gout should if possible be kept below 360 umol/L(6.0 mg/dL) (EL III)(7). * Reduce dietary purine intake and restrict alcohol.

- Increased renal excretion of urate by uricosuric drugs, which decrease the reabsorption of uric acid from kidney tubules. Eg, probenecid
- Reduce urate production by allopurinol, an analog of hypoxanthine. Allopurinol is a competitive inhibitors of xanthine oxidase thereby decreasing the formation of
- uric acid. Xanthine and hypoxanthine are more soluble and so are excreted more easily. Xanthine oxidase converts allopurinol into alloxanthine. It is a more
- effective inhibitor of xanthine oxidase. This is a good example of suicide inhibition. Allopurinol was synthesized by Elion and Hitching independently.
- Colchicine, an anti inflammatory agent is very useful to arrest the arthritis in gout.
- Use of PEG -uricase and conversion of uric acid to allantoin is also being tried as a therapeutic measure to reduce body uric acid pool(TB).

Conclusion

Serum urate levels should be lowered enough to promote dissolution of urate deposits in patients with tophaceous gout. Allopurinol and benzbromarone are equally effective when optimal serum rate levels are achieved during therapy. Combined therapy may be useful in patients who do not show enough reduction in serum urate levels with single-drug therapy. By understanding the causes and pathophysiology of hisperuricemia and gout, have led to the development of effective therapies.

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