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Review

Gout: An old disease in new perspective – A review

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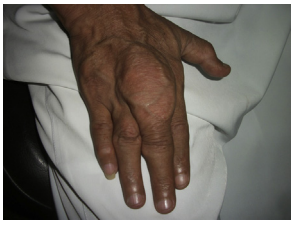
GRAPHICAL ABSTRACT



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ABSTRACT

Gout is a picturesque presentation of uric acid disturbance. It is the most well understood and described type of arthritis. Its epidemiology is studied. New insights into the pathophysiology of hyperuricemia and gouty arthritis; acute and chronic allow for an even better understanding of the disease. The role of genetic predisposition is becoming more evident. The clinical picture of gout is divided into asymptomatic hyperuricemia, acute gouty arthritis, intercritical period, and chronic tophaceous gout. Diagnosis is based on laboratory and radiological features. The gold standard of diagnosis is identification of characteristic MSU crystals in the synovial fluid using polarized light microscopy. Imaging modalities include conventional radiography, ultrasonography, conventional CT, Dual-Energy CT, Magnetic Resonance Imaging, nuclear scintigraphy, and positron emission tomography. There is remarkable progress in the application of ultrasonography and Dual-Energy CT which is bound to influence the diagnosis, staging, follow-up, and clinical research in the field. Management of gout includes management of flares, chronic gout and prevention of flares, as well as management of comorbidities. Newer drugs in the pharmacological armamentarium are proving successful and supplement older ones. Other important points in its management include patient education, diet and life style changes, as well as cessation of hyperuricemic drugs.

Introduction

Gout distinguished itself in the history of Homo sapiens since time immemorial. It appeared in medical records very early in the history of medical writing, and was also mentioned in the biographies of many famous names. It was depicted as the fate of a life of affluence as much as the challenge to a physician's skill, and truly it was. Modern ages witnessed remarkable progress in managing gout. More recently, thanks to quantum leaps in molecular biology, diagnostic modalities, and pharmacotherapy, we enjoy deeper understanding of the disease and a more sophisticated armamentarium.

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Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop gout or even form UA crystals. In fact, only 5% of people with hyperuriceamia above 9 mg/dL develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout [1,2].

MSU crystals can be deposited in all tissues mainly in and around the joints forming tophi. Gout is mainly diagnosed by identification of the pathognomonic MSU crystals by joint fluid aspiration or in tophi aspirate. Early presentation of gout is an acute joint inflammation that is quickly relieved by NSAIDs or colchicine. Renal stones and tophi are late presentations. Lowering SUA levels below deposition threshold either by dietary modification and using serum uric acid lowering drugs is the main goal in management of gout. This results in dissolution of MSU crystals preventing further attacks [3,4].

Epidemiology

The general prevalence of gout is 1–4% of the general population. In western countries, it occurs in 3–6% in men and 1–2% in women. In some countries, prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than 80 years old. Annual incidence of gout is 2.68 per 1000 persons. It occurs in men 2–6 folds more than women. Worldwide incidence of gout increases gradually due to poor dietary habits such as fast foods, lack of exercises, increased incidence of obesity and metabolic syndrome [5].

Pathogenesis of hyperuricemia

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dL [1,6].

Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolytes level, and other synovial components such as proteoglycans and collagen. SUA level in the body is determined by the balance between its production either from purine intake in diet or endogenous production by cellular turnover and its excretion by the kidneys and GIT. Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under-excretion [7].

Factors affecting SUA levels include age and gender. SUA is low in children. After puberty, SUA levels start to increase to reach their normal levels. In men, levels are higher than in women. However, SUA levels in postmenopausal women increase to reach men's levels. This explains why gout is usually a disease of middle aged and older men, and postmenopausal women. Rarely, it may happen in children and young adults in some rare inborn errors of purine metabolism. These enzymatic defects result in increased SUA with consequent production of UA crystals in kidneys and joints (Fig. 1) [8].

Overproduction of uric acid

Deficiency of enzymes involved in purine metabolism leads to overproduction of UA. For example, Lesch-Nyhan syndrome is an inborn error of metabolism resulting from deficiency of an enzyme involved in UA metabolism named hypoxanthine–guanine phosphoribosyltransferase. It is a genetic X-linked recessive disorder with varying degrees of severity according to the type of mutation. The clinical picture of this disease involves neurological abnormalities such as dystonia, chorea, cognitive dysfunction, compulsive injurious behavior, self-mutilation and articular manifestations (early onset gout) in addition to renal stones. If left untreated, it may lead to tophi formation and renal failure [9].

Another enzymatic abnormality that causes gout in the young is the superactivity of phosphoribosyl pyrophosphate synthetase. It is an X-linked dominant inherited disorder. The syndrome has two clinical forms, a severe early onset form in children and a mild late juvenile or early adult onset form. Clinical picture includes neurological abnormalities such as sensorineural hearing loss, hypotonia and ataxia in the severe form. The mild form manifests as uric acid renal stones and arthritis. However, these enzymatic disorders constitute only less than 10% of cases of overproduction of urates [10].

Diet

Ingestion of foods rich in purines such as cooked or processed food especially from animal and seafood origin is a key element of increasing uric acid precursors. While foods rich in purine of vegetable origin such as beans, lentils, mushrooms, peas, legumes, and dairy products do not carry any risk on hyperuriceamia and gout, thus, can be allowed in gout patients. Furthermore, foods rich in vitamin C, low fat dairy products, plant oils such as olive, sunflower and soy were associated with reduced risk for hyperuriceamia and gout. Vitamin C was found to increase renal excretion of uric acid so it can be used as a supplement during management of gout [11,12].

Alcohol is a well-known risk factor for gout. Studies showed that alcohol consumption is related to the amount consumed. Additionally, the risk for gout and hyperuriceamia depends on the type of different alcoholic drinks. For instance, beer is the worst in increasing the risk for gout compared to liquor. While the lowest risk among alcoholic drinks was for wine [11].

Endogenous urate production

Increased endogenous production of uric acid occurs in accelerated cellular turnover such as in malignancies, heamatological and inflammatory diseases. Also, increased purine production may result from chemotherapy and tissue damage. Furthermore, increased body weight and obesity leads to enhanced production of uric acid aggravating the risk of hyperuriceamia. Leptin was found to increase serum levels of urate. So, weight loss and exercises are very useful in reducing SUA levels and gout risk [13–16].

Decreased excretion of uric acid

Two thirds of urate excretion occurs in the kidneys while the rest is excreted through the gastrointestinal tract (GIT). Reduced secretory function of the transporter ABCG2 leads to decreased excretion of uric acid through the GIT resulting in rise of serum levels of uric acid and enhanced renal excretion[7,17].

Uric acid crystals are not soluble so require specific membrane transporters in order to cross cell membranes. Of these transporters are the urate transporter/channel (URAT) mainly URAT1 and the organic anion transporters (OAT1 and OAT3) [7,18].

Renal excretion of uric acid is the end result of 4 phases. The first phase is the passage of UA across the Bowman's capsule (glomerular filtration); followed by reabsorption of almost all urates passing in the proximal tubules. The third phase involves secretion of part of the reabsorbed UA ending with another reabsorption phase in the proximal tubules. The excreted UA is almost 10% of the filtered urate through Bowman's capsule and the rest is reabsorbed in the body (Fig. 2) [19].