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Review Article

New Developments for Gout

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Abstract

In this mini-review new developments for gout are discussed. Whole genome studies show that genetic drivers in gout are far more important than diet, as once believed. It has become obvious from new studies that there is a definite relationship between gout and the 'residual arterial inflammation of atherosclerosis'. Interleukin-1-beta plays a central role in this relationship, raising new interest in colchicine, the anti-gout drug and IL-1 beta production blocker, and niacin. The CANTOS study provided clinicians with evidence that targeting inflammation with the IL-1-beta antagonist canakinumab is beneficial for the secondary prevention of atherosclerosis and reduces gout attacks by 50%. Further whole genome and exome studies will lead to better anti-inflammatory therapies for gout and atherosclerosis.

Introduction

Gout is the most common inflammatory arthritis and its incidence in the U.K. has steadily increased from 1,5% in 1997 to 2,5% in 2012. It is characterized by deposition of monosodium urate crystals in joints and tissues and usually presents with intermittent painful attacks followed by long periods of remission [1]. In the U.S. gout affects about 4% of American adults,or about 8,3 million individuals [2].

For centuries, gout has been blamed primarily on people's dietary choices, particularly too much red meat and alcohol [3]. However, recent studies found that genes plays a much larger role in the development of gout than diet. Gout research also suggest interplays with cardiovascular disease. In the CANTOS trial canakinumab showed to reduce gout in more than half in atherosclerosis [4]. In this mini-review pathophysiology, genetics and the role of gout in cardiovascular disease will be discussed.

Pathophysiology

Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a threshold is a requirement for the formation of uric acid crystals. However, many people with hyperuricemia do not develop gout or even form UA crystals. Only 5% of people with hyperuricemia above 9 mg/dl develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout [5,6]. MSU crystals can be deposited in all tissues mainly in and around the joints forming tophi. Gout is diagnosed by identification of the pathognomic MSU crystals by joint fluid aspiration or in tophi aspirate.

Gout presents usually as an acute joint inflammation that is quickly relieved by non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine. Renal stones and tophi are late manifestations. Lowering SUA levels below deposition threshold either by dietary modification or serum uric acid lowering drugs is the main goal in the management of gout. This results in dissolution of MSU crystals preventing further attacks [7,8].

The general prevalence of gout is 1% to 5% of the general population. In some counties prevalence may increase up to 10%. Gout occurs 2-6 folds more in men than in women. Annual incidence of gout is 2,68 per 1000 persons. Worldwide incidence of gout increases gradually due to poor diet habits such as fast foods, lack of exercise, obesity and metabolic syndrome [9].

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5,8. Pathological threshold of hyperuricemia is defined as 6,8 mg/dl [5,10]. Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolyte levels 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 the gastrointestinal tract. (GIT).Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under secretion [11].

SUA levels are affected by age and gender. Levels are 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 increase to reach men's levels. This explains why gout is usually a disease of middle aged, older men and postmenopausal women. Rarely, it happens 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 [12].

Increased endogenous production of uric acid occurs in accelerated cellular turnover such as in malignancies, hematological and inflammatory diseases. Also, increased purine production may result from chemotherapy and tissue damage. Increased body weight and obesity leads to enhanced production of uric acid, aggrevating the risk of hyperuricemia. 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].

Two thirds of urate excretion occurs in the kidneys while the rest is excreted through the GIT. Reduced function of the transporter ABCG2 leads to decreased excretion of uric acid through the GIT resulting in a rise of serum levels of uric acid and enhanced renal excretion [11,17]. Uric acid crystals are not soluble so they require specific membrane transporters in order to cross cell membranes. Of these transporters are the urate channel transporter (URAT),mainly URAT1 and the organic anion transporter OAT1 and OAT3 [11,18].

Renal excretion of urate is by glomerular filtration, followed by reabsorption of almost all urates passing in the proximal tubules. Secretion of part of the reabsorption of the urate occurs when the tubular maximum for reabsorption is exceeded. The excreted UA is almost 10% of the filtered urate and the rest is reabsorbed in the body [19].

Reduced renal urate excretion is associated with some autosomal dominant disorders. Uromodulin is a gene that is expressed in the thick ascending limb of the loop of Henle and regulates water permeability. Mutations of uromodulin gene results in decreased fractional excretion of UA, which in turn increases SUA [20].

URAT1 transports UA in the filtered fluid passing through the proximal tubules into the tubulules by an active transport process. Uricosuric drugs such as probenecid, benzbromarone and sulfinpyrazone decreases URAT1 activity, and consequently UA reabsorption in proximal tubules. On the other hand, drugs such as pyrazinamide, nicotinate and lactate increase urate reabsorption by acting on URAT1,moving UA from the lumen into the tubular cells. They both increase glomerular filtration and tubular reabsorption of UA preventing its loss in urine and increasing UA levels in serum [21].

Substances that affect UART1 activity can both potentiate or inhibit URAT1 activity according their dose. For example, low doses of aspirin have an anti-urocosuric effect while high doses have a urocosuric effect. This is called cis-inhibition of URAT1 and trans-stimulation of URAT1 by aspirin [22].

Genetic Drivers for Gout

Serum urate concentrations exhibit a strong genetic predisposition with a heritability estimate ranging from 40% to 70% [23-25]. SLC22A12 gene encodes for the transporter URAT1 present on the apical membrane of renal tubules. SLC2A9 is another gene encoding for an urate transporter protein. Polymorphism of both genes result in decreased fractional excretion of UA leading to increased SUA levels. ABCG2 is a gene transporter for UA in the proximal tubular cells of the kidney as well as in the GIT. SLC17A1,SLC17A3 genes are important determinants of SUA levels acting as membrane transporters in the kidneys.

Other genes involved in determination of SUA levels include SLC22A4,the glucokinase regulatory protein (GCKR), Carmil (LRRC16A) and near PDZK domain containing1 (PDZK1) genes [23-25].

Recently, Major *et al.* performed a meta-analysis of data collected from 8414 men and 8346 women from five U.S. studies. All the participants were aged 18 year or older, and none had kidney disease or gout. Nor, were any of them taking prescription drugs known to affect uric acid levels, such as diuretics [26]. The data included genetic profiles and measurements of urate and detailed food questionnaires.

This meta-analysis found that high serum urate levels were associated with seven foods: beer, wine, liquor, potatoes, poultry, soft drinks and meat (beef, pork or lamb). Reduced SUA levels were associated with eight foods: eggs, peanuts, cold cereal, skim milk, cheese, brown bread, margarine and non-citrus fruit. But each of these foods explained less than 1 percent of the variation in the participants' urate levels. The researchers then looked at the participants' entire diets. Healthy dietary guidelines, such as the DASH diet, was associated with lower urate levels, while following a diet high in unhealthy foods was linked with higher urate levels. By contrast, when the authors did their genetic analyses, they found that common genetic factors among the participants explained almost a quarter (23,9%) of the variation in their urate levels. These findings held even after adjusting for factors that can affect urate levels, such as age, body mass index (BMI),daily caloric intake, exercise habits and smoking status.

This study has some caveats. It used different questionnairres in the 5 studies investigated, participants were U.S. citizen of European ancestry and none had gout. So the findings may not be generazible to more ethnically different populations or to people with gout. Dong *et al.* explored two genetic pathways influencing SUA levels and gout risk in a Chinese population meta-analysis in 2018 [27].

These recent meta-analysis findings support other research involving twins and families that has suggested genetics explains at least 25% to 60% variability in serum urate (SUA) levels [1,2,23-25,27].

Anyway, if patients ask if gout is genetic?, the answer is Yes, and is drinking beer the cause of my gout?, the answer is No. Do these findings change the management of gout? Not in the short term. However, it will be interesting to see how these genetic drivers for gout relate to the observed 50% decrease in gout in the CANTOS trial [4].

Gout and Atherosclerosis

In a recent large scale study Duke University researchers assessed the contemporary association between gout and cardiovascular disease in patients with obstructive coronary artery disease [28]. They followed patients undergoing cardiac catheterization for obstructive (CAD) between 1998 and 2013 (n=17.201 patients). The relationship was assessed between gout at baseline or during follow-up and the primary composite outcome of cardiovascular death, myocardial infarction, or stroke, adjusting for differences in baseline clinical factors. Secondary end points included cardiovascular death and all-cause mortality. New, post-baseline gout diagnosis was included as a time-dependent covariate.

Among 17.201 patients,1406 (8,2%) had baseline gout and a high burden of cardiovascular risk factors, but high rates of optimal medical therapy. Over a median follow-up of 6,4 years gout diagnosis was not associated with the primary outcome (HR;95%CI;1,05 (0,96-1,15);p = 0,31) or cardiovascular death (HR;95%CI;1,10 (0,99-1,22);p < 0,08),but was associated with increased all-cause mortality (HR;95%CI;1,13 (1,05-1,23);p = 0,002). After including new post-baseline gout diagnosis, the instantaneous risk of the primary outcome was significantly associated with prior gout diagnosis (HR;95%CI;1,15 (1,07-1,25);p =0,0004.

This large retrospective study shows that a clinical history of gout is associated with worse outcomes in a contemporary population of patients with obstructive CAD. This increased risk exists despite high levels of optimal cardiovascular medical therapy, supporting the concept of 'residual arterial inflammation' in atherosclerosis [4,29].

About 50% of patients develop atherosclerosis in the absence of hypercholesterolemia due to putative antigens as e.g nicotin, heat shock proteins, components of lipoproteins (Lp's) and various microbial structures, inducing an inflammatory process, that on its own may generate the atherosclerotic plaque formation [29,30]. Therefore, even with intense LDL-C reduction a cardiovascular risk remains. New cellular pathways, including gout, that may explain how arterial inflammation develops are explored.

Interleukin-1-beta IL-1-beta) plays an important role in these pathways raising new interests in the anti-gout drug colchicine and niacin. With the CANTOS results, clinicians have evidence that directly targeting inflammation by the IL-1-beta antagonist canakinumab is beneficial for the secondary prevention of cardiovascular disease. Whole genome and exome studies will soon lead to the discovery of new cellular pathways and treatments of residual arterial atherosclerotic inflammation [29]. These new developments for gout certainly will help in the further elucidation of the concept of 'residual arterial atherosclerotic inflammation'. As we look to the future, further whole genome and exome studies are needed to discover how these new cellular pathways in gout and atherosclerosis play together, leading to better anti-inflammatory therapies for gout and atherosclerosis [28,29].

Conclusion

New developments for gout show that genetic drivers are far more important than diet, as was once believed. It has become obvious that there is a definite relationship between gout and the 'residual arterial inflammation of atherosclerosis' [4,28-30]. IL-1-beta plays a central role in this relationship, raising new interest in the anti-gout drug colchicine, an IL-1-beta production blocker, and niacin. The CANTOS study provided clinicians with evidence that targeting inflammation by canakinumab is beneficial for the secondary prevention of atherosclerosis and also reduces gout attacks with 50%.Further whole genome and exome studies in gout and atherosclerosis are needed to discover new cellular pathways in both diseases, leading to better anti-inflammatory therapies for gout and atherosclerosis [28,29].

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