Review Article

Gout: Causing Factors and Counter Strategies

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Abstract

Gout is an inflammatory arthritis caused by hyper-uricemia in blood. It mostly occurs in the middle or later part of the life, so considered as the arthritis of elders with increasing frequency in current years about 1−2% of the Western part of the world. Generally, it is characterized by repeated attacks of acute inflammatory arthritis (a red, tender, hot, swollen joint) and first clinical manifestation of gout is inflammation of (big toe) 1st metatarso-phalangeal joint. It may present with subcutaneous or intra articulate tophi, kidney stones or urate nephropathy caused by increased levels of serum uric acid which crystallize and are deposited in joints kidneys and other soft tissues. Uric acid is a by – product of purine metabolism, being broken down by the action of xanthine oxidize enzyme into soluble allantoin easily excreted through kidneys. Hyper-uricemia may be due to over production of uric acid or may be due to under – secretion of uric acid resulting in gouty arthritis. Diagnosis mostly established by lab tests, high resolution ultra-sonography, MRI, CT scans of joint, kidneys and other soft tissues for hyper-uricemia, and for the visualization of the uric acid crystals / stones. Treatment strategies may includes non-steroidal anti-inflammatory drugs (NSAIDs), steroids, colchicines, changes in life style and dietary habits improve the symptoms of inflammation. After an acute attack of gout the levels of uric acid can be lowered by modification in lifestyle in the form of appropriate exercise therapy and by taking DASH diet. In those with frequent attacks allopurinol or febuxostat provides prevention in long run. Advanced therapies have been attempted such as Egloticase as well role of vitamin C is very important in the prevention and treatment of gout.

Key Terms: Hyper-uricemia, Monosodium urate crystals, Uricase, DASH diet, Exercise.

Introduction

There are numerous inflammatory diseases which can affect humans in their later part of life, but gout is mostly occurring disease in men in their middle or later part of life. Gout is stimulated in the presence of monosodium urate crystals in the synovial joint cavity. The most salient feature of gout is chronic hyperuricemia, which can be defined by the presence of excess of serum uric acid level more than 7 mg/dl.[1] So, (2008)[2] and Perez-Ruiz et al. (2009)[3] demonstrated that it is an inflammatory response which is initiated and accelerated by the increase concentration of monosodium urate crystals in the synovial joint, usually effects single joint so it is also known as mono-arthritis which shows sign of inflammation. First meta-tarsophalangeal joint is mostly involved in gouty arthritis.[4] In acute phase, the affected joint shows signs of acute inflammation with the presence of tender nodule

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termed as tophi.[5] In past few years, the prevalence of gout is significantly increasing in older population[6 7] Mostly, it is linked with metabolic syndrome, hypertension and congestive heart diseases.[7]

Unfortunately, no appropriate guidelines are available in Pakistan for the diagnosis and pharmacological and non pharmacological treatment options for gout. Medical practitioners manage gout on the basis of their clinical experience or expert opinion or they merely use pharmacological interventions. The current review will elaborate gout and it's causing factors and will also reveal the advanced diagnostic and pharmacological / non pharmacological treatment options for gout.

Epidemiology and Genetics Influence

Recently in retrospective study about the prevalence of gout in European countries shows that there were 34071 individuals in the UK and 34797 in individuals in Germany suffered from gout, demonstrating the gout incidence is about 1.4% in these countries.[8] Generally the gout incidence rate is about 1% but in some part of the world it has higher incidence rate like in New Zealand and Marois with 3.6% and 6.4% simultaneously.[9] In other project by Wrights et al., (2007)[5] demonstrated that, the gout prevalence rate is increased with increasing age and it is more frequently occur in men as compared with women.

Recently, researchers[10] had reviewed the different studies about the prevalence and incidence rate of gout. A study was performed in 1967 by means of Framingham data indicated that the prevalence of gout is about 1.5% in western part of the world. In England it was estimated 0.26% in 1975, and in another study showed increasing prevalence of gout in 1995 up to 0.95%. Moreover, some studies[11] showed that prevalence of gout is increasing day by day in USA and other part of the world. The most current longitudinal cohort study demonstrated that the prevalence of gout is increasing especially in men with rate of 8.6%. Another study[1] determined that gout is becoming serious problem day by day. It is dietary associated disease and its prevalence rate is about 1% in European part of the world.

Genetic Factors

There are many reasons for the high level of serum uric acid. It may be due to renal impairment, when kidney fails to excrete uric acid at normal level or endogenous over production.[21,27] Sometimes, there are genetic factors also involved in the development of Gout in the form genetic mutation in $GLUT_9$ gene besides these dietary or metabolic problems. Presently, there are many studies which showed that the mutation in the $GLUT_9$ gene have marked influence on the serum level of uric acid (UA). They had conducted study using 665 individuals using standardized questionnaire, physical examination, and biochemical study for data collection with the diagnosis of gout and 665 healthy controls without gout with matched age and gender and family history of Coronary arterial disease (CAD) and Myocardial infarction (MI), having four single nucleotide polymorphisms SNPs. They showed marked affinity with the development of gout. Factors, SNP rs6855911 and rs7442295 had found more involvement with serum Uric Acid levels. They also tested cases of coronary arterial disease and myocardial infarction with the GLUT9 as well. They had found that the normal genetic mutation in GLUT9 gene have more effect in the form of myocardial infarction or coronary arterial disease but surprisingly they also found that these mutation can also a common risk factor in the development of gout.[1]

Normal Physiology, Pathophysiology

Uric acid is generally considered as the byproduct of the purine metabolism and it is produced as a result of the conversion of xanthine, with the help of xanthine oxidase enzyme.[2,7,12,21] By the Practical prospectus, it is caused not only because to over-production of uric acid but it is due to of under – secretion of urate.[7,26] The levels of Uric acid are normally estimated by endogenous metabolism and the rate of renal excretion and re-absorption.[7,12,23] Recently one study showed that the mammals have more concentration of uricase enzyme as compared with concentration of uricase enzyme in human. Uricase enzyme plays a key part in conversion of uric acid into allantoin. So, due to this factor human have more uric acid level. Normally plasma urate level lies in range of 3.3 to 6.9 mg/dL.[23] The mono sodium urate is present abundantly in plasma and has solubility near to 7 mg/dl.[1] Due to the shortage of uricase enzyme that plays a major role in converting uric acid into more soluble and excretable allantoin form which is excreted by the kidneys. This shortage leads into hyperuricemia and gout in human population.[1,12] Apart from this, urate transport proteins like the human UR-

AT_1 transporter and the fructose transporter SCL_2A_9 mostly consider for maintenance and managing uric acid level, any fluctuation, disturbance or mutation in subsequent genes resultsinto the impaired function of the transporters and decreased urate excretion by the kidneys. As a result of this, there is addition of urate, which is a key factor in the development of the gout. The urate transport function is influenced by a range of drugs as well. Different diuretics decrease excretion of urate by blocking the $hURAT_1$ transporter protein. Once uric acid amounts exceed its saturation point of 400 µmol/L, it comes out and leads to deposition and accumulation of monosodium urate crystals in joints and soft tissues resulting in inflammation of joints[7]. Mono sodium Urate crystals in soft tissues results into inflammation. At the site of the inflammation, there is aggregation of neutrophils due to chemo tactic factors and release of pro-inflammatory cytokines which in turn aggregating more polymorphonuclear neutrophilic granulocyte. Interleukin 1, 8, 18 and TNF mostly involved in inflammation.[7,13]

Recently some studies[1,13] have shown that, the pain and inflammation are related with IL_1. In the same manner patient with gouty arthritis in acute condition get relieved by blocking IL_1 with different agents. These facts show that these cytokines have prime importance in the development of gout and related inflammation. The urate crystals help in the activation of these pro inflammatory cytokines which in turn, they lead to inflammatory conditions. Different conditions like Hyperuricemia, obesity, hypertension, diuretic use, andalcohol consumption are the prime risk factors that contributed in the development of gout.[2,12]

Clinical Features

Inflammatory Arthritis

The prime classical presentation is an early occurrence of mono-arthritis, especially at the first MTP joint of the large toe with pain and swelling. Intense pain in early stage remains about seven days and usually it is self remitting condition.[7] The deposition of monosodium urate crystals in joint causes the inflammation in the joint by activating the pro inflammatory cytokines. There is more deposition of urate crystals in the joints, there will be more inflammatory response in the relevant joint.[7,13]

Neurological Involvement

Karp et al., (2006)[14] found that, the Neurological and psychological disorder and symptoms linked with gout like sleep difficulties, pain, depression, decreased mobility because of lethargy and use of opioids for pain control has profound result on cognition. With increasing age, adults suffered more and at higher risk of cognitive impairment from pain and opioids, which in turn further decline in cognitive abilities. Ultimately, these factors lead to the older people to clinical dementia and functional dependence.

Diagnosis

Diagnosis of gout is generally based on history of patient (personal and family history), physical examination, sign and symptoms, laboratory and radiological finding. American rheumatism association formulates the criteria for the diagnosis of gout. The criteria of American rheumatism association are based on the finding of clinical, laboratory and radiological analysis. The clinical finding for diagnosis of gout includes repeated attack of acute arthritis with marked sign of inflammation mainly in 1stmetatatarso-phalangeal joint unilaterally. Laboratory finding includes hyper-uricemia presence of tophi, and negative fluid culture during early phase of disease. Radiological finding includes swelling within joint and presence of sub-cortical cysts without erosion.[5] Complete history of the patient including disease and diet history, physical and clinical examination, laboratory evaluation and radiological assessment are the basis for the assessment and diagnosis of the gout.[5,7]

Lab diagnosis is an important instrument to investigate and for the diagnosis of the gout, but one thing should be kept in mind that during early stages of gout, some time there is normal or low level of serum urate level.[25] So, to avoid this error tests should be performed 2 – 3 weeks after an acute symptoms of the gout. On the other hand, joint puncture is another test to evaluate the presence of urate crystals in the joint.[7] The laboratory tests used to investigate the gout are normally used after taking history of the patient. Usual laboratory tests used in clinical practice for establishing diagnosis may consists of full blood count, erythrocyte sedimentation rate (ESR), renal and liver function test (RFT and LFT), c reactive protein (CRP), serum urate and creatinine. In the first phase, ultrasonography is useful but in later stages joint puncture is used to see the severity of the condition.[5,7]

Researcher[5] demonstrated that scans by using high resolution ultrasonography of 1st metatarsophalangeal joint in both longitudinal and transverse planes for assessing the gout condition. Each sonographic stored picture digitally that provides the information about the single to multiple erosions of joint. It also provides exact information about the location of theerosions, whether they are located medially or on dorsal side. Ultrasonography also helps in identification of unifocal or multifocal lesions. It also gives information regarding soft tissue involvement. The sign of Joint inflammation can be detected by the presence of joint effusion or by the increase the amount of synovial fluid in joint cavity.

MRI helps in timely recognition of tophi, synovial involvement and wearing of bone in gout patients. It has been demonstrated that urate deposits mostly disseminate beside the compartmental and facial planes in spite of radial planes. Computerized tomography (CT) scan is another tremendous tool of identification of subcutaneous and intra-articular tophi.[3]

Treatment of Gout

Anti-hyper-uricemic therapy is recommended in case of chronic hyper-uricemia and in those patients who suffered from recurrent gout attacks for more than two years.[15,22] Gout and chronic hyper-uricemia incidence is increasing day by day due to many factors.[24] Renal impairment, hypertension, cardiovascular disorders, metabolic disorders and extra usage of diuretic medication are the main factors which contribute in the development and formation of the gout. Allopurinol generally used urate – lowering drug now a days, but its effectiveness is limited or restricted, because patient with renal impairment cannot tolerate its normal dosage and hence fail to lower serum uric acid level by using low or sub therapeutic dosage. Allopurinol may cause different gastrointestinal, hepatic, renal, hematological disorders and skin toxicities. Due to Allopurinol side effects an alternative medicine xanthine oxidase inhibitor with the brand name febuxostat is suggested and approved recently, which does not require dose management in mild to moderate renal disorder and impairment.[7,15,19,28] The safety and efficacy of Febuxostat is assessed by Becker et al. (2010).[16] They had found that's its effect more positively with low dose on serum uric acid level as compared with allopurinol. They demonstrated that, Febuxostat is more effective and much safer anti hyperuricemic drug as compared with allopurinol or others drugs used in hyperuricemia.

Inflammation of joints is the hallmark of acute attack of gout. Inflammation is managed usually now a day by the administration of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and colchicines. These drugs inhibit inflammatory mechanisms effectively. Now a day's COX_2 – selective inhibitor administration is very effective way in managing inflammatory conditions in early stages of gout. Glucocorticosteroid therapy is very effective in patient with renal impairment in early course of gout disorder. Especially prednisolone 35 Mg / day / for five (5) days compared with naproxen 500 mg two times daily for 5 days have better results in early stages of inflammatory condition in gout. Prednisolone is also better choice with good efficacy than indo-methacin.[19] Colichine is another drug of choice which can be used in gouty arthritis but it is used rarely and in Low dose to avoid its adverse effects on gastrointestinal tract. Higher dosage may cause gastrointestinal toxicity and diarrhea.[7,19]

Uricase oxidase is an important key enzyme which converts uric acid to soluble allantoin. This soluble allantoin is much more soluble as compared with uric acid and excreted easily through kidneys. Various uricase advanced therapies have been exercised such as Egloticase (uricase enzyme) with dose of 8 mg by means of intravenous infusion every 2 weeks has suggested these days. It metabolizes uric acid and converts uric acid into soluble allantoin with hydrogen peroxide and carbon dioxide as oxidative by products. Thus helps in removal of uric acid through kidney.[2,7,15] Ganson et al., (2006)[17] found the role of PEG – uricase as effective anti-hyperuricemic drug. They also found its effectiveness in soft tissues deposition of urate crystals. PEG – uricase is a new developing effective therapy, especially for those patients who have some renal impairment and drugs intolerance due to its adverse effects. PEG – uricase used in this clinical trial as anti-hyperuricemic drug but still needs further research to check its efficacy and specificity in hyperuricemic patients.

Along with pharmacological interventions, physical therapy and diet therapy plays an important role in the prevention and management of Gout. Life style changes like lose of extra weight, regular aerobic exercises, use of DASH diet, skimmed milk intake, less use of meat (low purine diet), no use of alcohol can draw positive changes in the management and prevention of gout.[9,29] In acute phase of gouty arthritis, electrotherapy in the form of lithium ionization is very effective because it forms soluble lithium urate instead of

insoluble sodium urate.[31] Moreover, cryotherapy and other non-thermal modalities are helpful in reducing pain and inflammation related with gout. In chronic cases, gentle massage, relaxed passive movement, active ROM and isometric exercises are very helpful in restoring patient normal activities of daily living.[30,31] Diet therapy is another non-pharmacological strategy to counter – measure gout. Researcher[18] found the association between vitamin C intake and the risk of development of gout. They had found that, the incidence of gout was more in persons who were using low amount of vitamin c in daily intake. The participants who were using higher vitamin C intake daily are at low risk of developing gout. So, gout can be prevented with proper intake of vitamin C and other nutritional strategies and adopting healthy life style.[30]

In short, there are numerous treatment options are available for the management of gout. Non pharmacological interventions should be prime choice for the prevention and management of gout. Regular aerobic exercise, intake of DASH diet and vitamin C is very vital for the prevention of gouty arthritis. Mild to moderate increase in uric acid level can be managed by appropriate physical and diet therapy. Pharmacological interventions like allopurinol or febuxostat provides prevention in long run. There are more need of research regarding the preventive measure and cure of the gout by means of nutritional strategies. Gene therapy is another field where further research is required to deal gout due to genetic factor involvement.

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