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Review Article

New Insights into the Epidemiology and Risk Factors Associated with Gout (Niqras)

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Abstract

Gout (Niqras) is an increasingly common chronic articular disorder characterized by abrupt attacks of severe pain and swelling (usually big toe), caused by the deposition of needle-shaped crystals of uric acid known as monosodium urate crystals around the joints. When the blood level of urate, the end product of purine metabolism, reaches its physiological limit of solubility, it may crystallize into monosodium urate (MSU) around the joints and raising the risk of both gout and renal stone. The traditional risk factors of male sex and high red meat, sea foods or alcohol consumption (especially beer) have been joined by a wave of newer risk factors, such as prolonged existence, congestive heart failure, hypertension, diabetes, dyslipidemia, overweight, use of certain medications (diuretics, low dose aspirin, cyclosporine), and renal problems. Gout affects at least one percent of the population in Western countries and is the most common inflammatory joint disease in men older than forty years of age. This article reviews new insights into the epidemiological data and comorbidities on this ancient disease.

Keywords: *Articular; Gout; Joint; Monosodium Urate Crystal; Niqras; Uric Acid*

Introduction

Gout is a disorder of purine metabolism characterized by acute, recurrent attacks of pain in a red, tender, hot, and swollen joint. Historically, gout is a disease of affluent, advanced aged men with overindulgent lifestyle, has now become more "democratic" by affecting more women and a wider range of socioeconomic individual groups. The global incidence and prevalence of gout appears to be growing for a variety of reasons, including iatrogenic ones. The recent dietary data shows the long-held relationship of gout with high consumption of alcoholic beverages and high levels of red meat ingestion but not with vegetables with high purine contents. Hyperuricemia (excess of uric acid in blood), predisposing condition for gout, is closely allied with the metabolic syndrome (over weight, hypertension, diabetes, dyslipidemia, increased risk of cardiovascular disease) and there is intensifying confirmation that hyperuricemia itself may be an independent risk factor for cardiovascular disease.

According to a recent study in UK, the overall prevalence of gouty arthritis to be 1.4 percent. The prevalence of gout rose with advancing age and was much higher among men.

The single most common risk factor for developing gout is a high serum uric acid level, with supersaturation of uric acid in the extracellular fluid compartment resulting in the precipitation of urate crystal around the different joints of the body. Deposition of urate crystals in the joint, surrounding the joint and subcutaneous tissues leads to episodes of acute arthritis and usually initially affects the first metatarsophalangeal joint (i.e. podagra). Additionally, deposition of these urate crystals in urinary tract may result in renal dysfunction. The primary objective in the treatment of chronic gout is to check crystal formation and promote crystal dissolution. According to European League against Rheumatism (EULAR), this is most efficiently achieved by reducing and maintaining serum uric acid levels below 6 mg/dl. Several research studies have proved that low serum uric acid level is linked with reduced frequency of gouty attack and reduction in tophi formation. The effective management of gout requires long-term administration of uric acid lowering medicines with regular serum uric acid level monitoring [1,2].

Epidemiology

Incidence

The incidence of gout varies in the population from 0.2 to 3.5 per 1000, with an overall prevalence of 2-26 per 1000. Gout is seen in only one-tenth of patients of hyperuricemia [3]. The prevalence increase substantially with age and increasing serum urate concentration [4-6].

The annual incidence rate of gout about 4.9% for serum uric acid levels > 9 mg/dl [4,7-9].

0.5% for values between 7 to 8.9 mg/dl, and 0.1% for values less than 7 mg/dl. For serum urate levels more than 9 mg/dl, the cumulative incidence of gout reaches 22% after five years [4,7,8,10-14]. The annual incidence of gout in men in most studies is in the range of 1 to 3 per 1000, but is much lower in women [15,16].

In the Framingham study, the 2 year incidence of gout was 3.2/1000 in men compared with 0.5 /1000 in women [17]. In a study in UK general population it has been establish that the incidence of gout per 1000 person years was 2.68 (4.42 in men and 1.32 in female) and increase with age [18]. Primary gout has hereditary features, with a familial incidence of 6-18% [19]. The incidence of primary gout doubled over the past 20 years, according to the Rochester Epidemiology Project [20].

Prevalence

In the general population, the prevalence of hyperuricemia ranges between 2 - 13.2%, and the prevalence of gout is between 1.3 and 3.7% [21]. Gouty arthritis is the most common variety of inflammatory joint disease in men over 40 years of age [3,6,21-23].

The overall prevalence of self reported gout in the general population is 0.7 percent to 1.4 percent in men and 0.5 percent to 0.6 percent in women [23].

In the National Health and Nutrition Examination Survey III, the overall men: women ratio ranged between 7:1 and 9:1. In ages younger than 65 rears, men had 4 times higher prevalence than women (4:1), but in older age groups (> 65) years, the gender gap narrow to 1 women for every 3 men with gout (3:1) [4,10].

The evidence from epidemiological data suggests that both the incidence and prevalence of gout have more than doubled over the last 40 years [3,4,11,14].

In UK general practice, for example the prevalence of gout is about 1.4% while SUA levels > 7 mg/dl are found in up to 18% of the population [5,11].

In a recent gout study in the United Kingdom, researchers found a prevalence of 2.49% and an incidence of 1.77 per 1,000 person-years in 2012, with both figures being higher than earlier estimates. Taiwan is one of the countries with the highest prevalence of gout worldwide [24].

Gout is rare in children and premenopausal women [3,14,22]. Children normally have a concentration in the rage of 3 - 4 mg/dl because of high renal uric acid clearance. At puberty, serum urate concentration increase by 1 to 2 mg/ dl in males. In contrast females show a little change in their serum urate level until menopause, when concentrations increase to approach the values seen for adult men [25].

There are about 5 to 6 million individuals of gout are present in the USA. This condition is more commonly seen in men than women, although among women the prevalence increases after menopause. In USA almost 12% of male aged 70 - 79 years affected compared with < 3% in men younger than 50 years [26].

The epidemiology of gout is changing due to alterations in the improving standard of living, lifestyle, drugs, weather conditions, seasonal changes and increase span of life. The ratio of male to female (which was 20:1 formerly) is now 2-7:1, or the prevalence rate /1000 in males 5-28, and1-6 in females. The annual incidence show a characteristic sex difference: 1-3/1000 in males and 0.2/1000 in females [27].

The previous research studies indicate that a variety of factors may influence the development of gout, including environmental, racial and hereditary factors [7,24]. Tokelaun migrants to New Zealand have more prevalence of gout than non-migrants [28].

Serum Urate level in south India are similar to reference ranges in Western countries.

Maori of New Zealand, Polynesians from Islands in the Pacific, some Chinese from Kinmen and Taiwan and aborigines from Taiwan have all been shown to have higher mean SUA level than other population groups [11].

Filipinos living in united state have a greater frequency of hyperuricemia and gout than other US men [4,11]. Urban South African Black had significantly higher Serum Urate level than those in a rural community [11]. African Americans have more hyperuricemia and gout than European Americans [4].

Badley and Desmeules reported that gout affect upto 3.0% of Canadian adults and men are four time more likely than women to develop gout. In New Zealand, the cumulative prevalence of self reported gout was 4.7% for persons 15 yrs and older of the Maori of the Arawa and Tuhoe tribes. A similar prevalence of 3.8% was found in the Yarrabah region of Australia. Other studies examining rheumatic conditions found a very low prevalence of gout ranging from 0.14% to 0.34% in Pakistan, Vietnam, Thailand, Mexico and China [29].

The Bhigwan COPCORD survey demonstrated low prevalence of gout (0.12%) in rural India. In another Indian study, gout prevalence of 2% was recorded. In study from Jammu only 2 cases gout were reported [10,30].

There is noticeable increase in incidence of gout in certain parts of India like Kerala in the recent years, quick urbanization with changes in lifestyle leading to obesity, lack of physical exercise; high protein diet, alcoholism and increasing use of drugs like thiazides are some of the cause for this rise in the incidence [11].

Some studies also suggest a seasonal difference in the occurrence of acute gout. Attacks are more frequent in the spring and autumn weather [31].

A study conducted in the Northern hemisphere, showed that acute gout flares occurred more often in the spring season. Arber., *et al*. established a higher incidence of gout in spring and summer, but McLeod in 1972 reported that a major number of Australian patients with gout suffered in autumn. The highest incidence of tophaceous gout is reported in spring season [32].

Risk factors

There are both no modifiable and modifiable risk factors for hyperuricemia and gout. Non modifiable risk factors include age and sex. Modifiable risk factors for gout include obesity, medication, high purine diet, alcohol etc [13].

Hyperuricemia

Hyperuricemia is the single most important determinant of the risk of developing gout. Development of gout depends on the degree of sustained hyperuricemia. The higher the initial urate level, the greater is the incidence of first episode of acute gouty arthritis [3,11,14,22,33,34].

Hakeem Mohammad Hasan Qarshi in "Jam-ul-Hikmat" mentioned that the chances of developing of Niqris is more in those having high level of Boli Mawad/Hamiz-e- Boli (Uric acid) in their blood and these Boli Mawad deposited in and around the joint [34].

Age

The incidence and prevalence of gout increase with age in men and women. Gout rarely occur under the age of thirty [11,31,33]. The incidence of gout, after the age of 60, between men and women is almost equal, and after the age of 80, women seem to predominate [35]. Ghulam Jeelani in "Makhzanul-Ilaj" and Samarqandi in "Asbab wa Aalamat" described that the incidence of Niqris mainly occur after 40 years [36,37].

Sex

The prevalence and incidence of gout are substantially higher in men than in women. Men are 10 time more likely to have gout than women. The fact that men have higher level of uric acid may explain their increased risk [11,22].

Dietary and lifestyle risk factors for the development of gout in men include a relatively high intake of meat, seafood and beer, with a protective effect in men associated with relatively high intake of low-fat dairy product [14].

Serum urate level increase by 1 to 2 mg/dl in men at the time of puberty, but women show a little change in their urate level until menopause, when concentration increase to approach the values seen for men [12].

It is hypothesized that estrogen is protective against urate deposition, by promoting renal excretion of uric acid [4,14,20,21].

In a recent population based study from South Korea, the prevalence of hyperuricemia has been reported to be 25.8% in males and 15% in females whereas 11.5% of males and 3% of females with hyperuricemia had gout [33].

In a recent nationwide survey (the Nutrition and Health Survey in Taiwan), researchers reported gout prevalence data of 8.2% in men and 2.3% in women in the period from 2005 to 2008 [24].

In the USA male veterans are at heightened risk for developing gout because of their numerous risk factors, as seen in the Normative Aging Study conducted by the US Department of Veterans Affairs [13].

The incidence of gout in female also increasing in India, due to increase longevity after menopause, changes in lifestyle and use of various hyperuricemic drugs [38].

According to Qarshi, renowned unani physician, prevalence of gout is higher in men comparatively to women [34].

Hypertension

There appear to be a link between gout and hypertension [11]. The Framingham Heart Study identified obesity and high blood pressure as risk factors for developing gout [39]. The incidence of gout in hypertensive women is low as compared to men. The risk of developing gout may be explained by hypertensive induced renal insufficiency, which can decrease uric acid clearance [40].

Iatrogenic

Kidney or heart transplant patients and patients on cyclosporine therapy are at an increased risk of developing gout. Gout develops in up to 10% of patients within the first few years following transplantation [4,11,15].

Kidney transplant recipients may develop increased levels of uric acid because its secretion diminishes with the decreasing glomerular filtration rate [13].

Medication

Commonly used medicines that may leads to hyperuricemia (too much uric acid level in the blood) by lessening renal urate excretion are loop or thiazide diuretics and aspirin (low dose). Other medicines include cyclosporine A, niacin, antituberculosis antibiotics, and didanosine.

Loop and thiazide diuretics (particularly in patients with heart failure or renal insufficiency) reduce uric acid excretion by causing mild volume depletion with consequent enhancement of proximal tubular reabsorption. Furosemide, nicotinic acid, and pyrazinamide may act directly on URAT 1 to enhance urate reabsorption. Ethambutol decrease renal urate excretion, aspirin in high doses (> 3 g/d) is uricosuric while low doses (1-2 g/d) elevate urate level.

Cyclosporine leads hyperuricemia in approximately 80% of transplant patients and develops gout in more than 10 percent of patients within a few years transplant.

Cyclosporine, calcineurin inhibitors, probably induces hyperuricemia via reducing renal tubular uric acid excretion and inhibiting glomerular filtration rates because of its ability to increase renal arterial vasoconstriction [4,10,11,13,20,22].

Local factors

There is some evidence that lower body temperature, lower pH and local connective tissue trauma can influence crystal formation [8,11].

Dietary factors

Dietary factors that leads to abnormally high uric acid in the blood include high alcohol intake (enhance purine production and reduce excretion of urate), eating a lot of foods rich in purines, especially meats and seafood and eating or drinking food and drinks high in fructose (a type of sugar). Fructose, widely rampant dietary factor, leads to hyperuricemia by accelerating the catabolism of adenine nucleotides.

Diets rich in purine (organ meat, shellfish) and high protein diets are generally considered risk factors for the development of gout. Recent studies have shown that diets enriched with dairy product, ascorbic acid confer a protective role. Research from the Third National Health and Nutrition Examination Survey (NHANES) found that higher levels of meat and seafood consumption were associated with

increased serum acid levels in adult, but total protein intake was not. A moderate intake of purine-rich vegetable is not associated with an increased risk of gout [4,41].

The risk of gout reduces relatively 40% - 50% in those consuming dairy products such as milk daily. Dairy proteins have a uricosuric urate-lowering effect. Consumption of sugar sweetened soft drinks, candy and fructose is also associated with increased risk of developing gout [11,13,14,42].

Whereas other protective factors include consumption of caffeinated coffee and high dose of vitamin C [4,43,44].

Other risk factors

Other risk factors include high body mass index, serum creatinine levels (renal insufficiency), central obesity, height, glucose intolerance, hypertension, diuretic use, low dose aspirin, family history, metabolic syndrome, hypertriglyceridemia, joint trauma, and unusual physical exercise. The connection of gout with obesity dates from ancient time [3,4,10,11,22,33,34].

Up to 76 percent of patients with gout have the metabolic syndrome. Hypertension itself can stimulate hyperuricemia, probably via increasing reabsorption of urate and reducing the renal blood flow. High uric acid is probably linked with glucose intolerance via the enhancing role of insulin resistance on renal urate absorption. High body mass index is also directly connected with hyperuricemia, leptin (a hormone) may be a contributory factor. Higher adiposity and weight gain are significant risk factors for developing gout, while weight loss is protective.

Hyperuricemia has been considered cardiovascular risk factor for a long time. Although there was no independent association between the two in Framingham study. In a recent review, it was concluded that SU is a moderate and independent cardiovascular risk and seems to be a higher risk factor amongst individuals already at higher risk for cardiovascular disease than in healthy individuals.

Patients with myloprolifertive disorders, polycythemia vera, myeloid metaplasia and chronic myelogenous leukemia, Bronchogenic Carcinoma, Hodgkin's disease, sickle cell anemia, Psoriasis are at increased risk because of the hyperuricemia from high cellular turnover [2,4,15,31].

Triggering factors

Provocative factors include surgery, trauma, infection, stress, dehydration, starvation, alcohol, dietary excesses, diuretics, pyrazinamide and aspirin [3,20,34,45].

Conclusion

Gout is the most common inflammatory condition, caused by elevated serum urate, in the United States. Several studies have demonstrated an increasing prevalence over recent decades. The incidence of gout (Niqras) has more than doubled over the recent twenty years. This increase together with the more frequent occurrence of comorbid conditions and cardiovascular (CVD) risk factors represents a major public health challenge. The apparent rise in the prevalence and incidence of gout over the recent years may be caused by growing populations with risk factors for this disease, such as high intake of purine-rich foods, obesity, diabetes, chronic renal disease, old age, use of diuretics, and organ transplant. Physicians and patients should be trained how to treat gout appropriately to lessen the unpleasant effects of medications.

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