

Comparing the etiologies, signs and drug treatments of gout: Literature review

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Gout affects millions of patients each year. This inflammatory arthritis results from elevated body uric acid, which leads to deposition of monosodium urate crystals mainly in joints. Since this condition can be affected by different factors within our lifestyles, modern medications have not been made to specifically target the causative factor. This article reviews recent literature by presenting the common etiologies and discussing drug innovations.

Keywords: gout, hyperuricemia, colchicine

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Affecting millions, gout has persisted throughout a long span of human civilization when first identified by the Egyptians and recognized by Hippocrates. It was thought to be a “disease of kings” due to its association with luxury foods and alcohol consumption, which were affordable to only the wealthy. Today, we know that gout is a form of inflammatory arthritis resulting from elevated body uric acid pool, which leads to deposition of monosodium urate (MSU) crystals mainly in joints [1]. Since this condition can be affected by different factors within our lifestyles, modern medications have not been made to specifically target the causative factor, which ultimately only suppress the symptoms. This article reviews recent literature by presenting the common etiologies and discussing drug innovations.

Methods

A thorough search of the published literature regarding (i) the epidemiology of gouty arthritis; (ii)

signs and lab results presentation; (iii) drug management for gouty arthritis patients; and (iv) new drugs on the rise. The searches were then prioritized on usage based on the date of publication and degree of relevance to the four topics mentioned.

Results

The epidemiology of gout can be characterized by its prevalence and risk factors such as diet, comorbidities, and heredity. The prevalence of gout among US was 3.9% (8.3 million individuals); 6.1 million men and 2.2 million women [2-4]. In terms of diet for gouty patient, fructose, red meat, and alcohol intake increases serum uric acid levels drastically. Major comorbidities within the population include obesity, renal disease, hypertension, and metabolic syndrome [1]. ATP-binding gene (ABCG2) and sodium-dependent monocarboxylate transporter gene (SLC2A9) showed significant association with development of gout [3]. Although radiologic

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evidence assists in the diagnosis of gout, the presence of MSU crystals with needle aspiration remains the gold standard [5-6]. Standard drug management of choice remains an NSAID (indomethacin) and colchicine for acute gout; regimen for chronic patient varies [7-9]. Research continues for the latest FDA approved drug Lesinurad as well as producing IL-1 inhibiting biological therapies [10].

Discussion

In terms of prevalence of gout among US, all relevant paper referenced the study data from NHANES 2007-2008 which estimated 6.1 million men and 2.2 million women have gout. Furthermore, the survey was compared to a previous data over the past two decades and presented an overall 1.2% increase prevalence of gout and 3.2% on hyperuricemia. Since the increase of hyperuricemia was greater, it is indicated that many people in the US are on the borderline of developing gouty arthritis. Possible overuse of diuretics and aspirin as well as comorbidities such as obesity and hypertension could attribute to that increase as well.

In most studies, hyperuricemia is classified when serum urate level is greater than 7.0 mg/dL. When purine-rich diet foods were compared, red meat and seafood produced significantly more purine and led to increased risk of gout incident as opposed to purine-rich vegetables and low-fat dairy products. Fructose degrades purine nucleotides and acts as a substrate for uric acid production, which increases the risk of gouty attacks. Consumption of sugar-sweetened soft drinks of two or more servings per day increases the risk of gout incident by an average of 106%. Alcohol consumption, particularly beer, is predispose to gout due to production of purine metabolic substrate guanosine, which enhances nucleotide turnover and impair renal urate excretion via lactic acidosis. Although moderate consumption of alcohol (2-6 oz/wk) did not affect increase gouty incident, those who drink two or more drinks per day had 2.5 times the risk.



Figure 1 Average percentage of comorbidities with gout.

On the other hand, coffee and vitamin C were examined and found to decrease gouty incidence due to their antioxidant properties that increase insulin sensitivity and enhance renal urate excretion. Additionally, caffeine is a methylxanthine that competitively inhibits xanthine oxidase, which is the major enzyme in purine metabolic pathway.

Since gout is created through the body's inability to decrease serum urate level, systemic comorbidities can potentially worsen and exacerbate the attack. Through 13 studies comparing comorbidities with gout, hypertension, dyslipidemia, cardiovascular disease, diabetes mellitus, and renal disease are all highly prevalent in individuals with gout. Hypertension was present in 40-74% of individuals with gout, dyslipidemia in 15-59%, cardiovascular disease in 13-41%, diabetes mellitus in 6-32%, and renal disease in 13-44% (Figure 1).

ATP-binding cassette subfamily G member 2 (ABCG2) gene produces the transporter that causes the export of uric acid out of the proximal tubules which overall decreases the intracellular urate concentration. With mutation of this gene, serum uric acid levels remain high and contribute to roughly 10% of individuals with gout. The gene SLC2A9, encodes a glucose/fructose transporter in the kidneys, which when coupled with the principal renal urate reabsorption transporter, will cause the excretion of urate from the tubule cells. Once again, a mutation within this specific gene will cause a decrease count of transporter produced to reduce urate levels in the serum.

Colchicine is a lipophilic alkaloid with short half-life but long actual half-life in plasma and metabolized by cytochrome P450. The anti-inflammatory effects can

disrupt microtubule function in activated neutrophils and prevent crystal-induced inflammation, which is why it's indicated as the initial drug of choice for gouty attacks. Colchicine can also be used as prophylaxis for gout patients (0.6 mg bid) for 90 days and indomethacin (50 mg tid) for 10 days. After administering colchicine to reduce acute inflammatory attacks, appropriate steps can be taken to determine if the patient is under-secreting or overproducing uric acid. Further medication can then be prescribed for each specific case:

- Indomethacin (NSAID) –analgesic, antipyretic, and anti-inflammatory by decreasing prostaglandin synthesis (50mg PO q8)
- Colchicine (Colcrys) – modulates anti-inflammatory pathways for gout, prevents microtubule assembly, and disrupts inflammasome activation (0.6-1.2mg PO initially, 0.6mg PO q1 until GI symptoms or pain relief; 0.6mg PO once daily or q12 as prophylaxis)
- Allopurinol (Zyloprim) – blocks uric acid production by inhibiting xanthine oxidase (100-600mg PO daily)
- Febuxostat (Uloric) – non-purine xanthine oxidase inhibitor (40-80mg PO daily)
- Probenecid (Benemid) – decrease uric acid reabsorption (250mg PO bid for 1 week, then 500mg PO bid)

Lesinurad (Zurampic) is the most recent FDA approved medication. It is the first selective uric acid resorption inhibitor and inhibits urate transporter-1 (URAT1), which promotes uric acid excretion. Additionally, lesinurad is indicated for hyperuricemia with gout patients that have not achieved target serum urate levels. This requires the drug to be co-administered with a xanthine oxidase inhibitor. Interleukin-1 is a pro-inflammatory cytokine that can mediate and initiate inflammation within the body. By creating inhibitors that specifically target the cytokine and inflammasome, gouty inflammations can be reduced.

Conclusion

Although the criteria for diagnosing and managing gout are beginning to solidify in modern standard of care settings, the results of this literature review demonstrate a need of long-term research with advancing technologies on new medications to understand their specific effects on the suppression of recurrent gouty episodes.

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