Volume : 5 | Issue : 4 | April 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Research Paper

Recent Advances in The Understanding and Management of Gout And Hyperuricemia: Myths and Facts

Medical Science

KEYWORDS :

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Introduction:

Hyperuricemia and Gout are hereditary disorders that involve abnormalities of nucleotide metabolism in which there is increased production or impaired excretion of a metabolic end product of purine metabolism (uric acid), leading to deposition of monosodium urate crystals (MSU) in supersaturated extracellular fluids, which leads to deposits in the articular and periarticular tissues causing erosive arthritis, in the cartilage and subcutaneous tissues in the form of Tophi. It can lead to uric acid nephrolithiasis, or interstitial nephropathy with renal impairment, characterized by a phase of acute attacks followed by remission and relapses. [1]

Causes/Promoters of Gout:

1. Gout occurs when excess uric acid (a normal waste product) collects in the body and needle- like urate crystals deposit in the joints either due to uric acid over-production or, more often, impaired urinary excretion of uric acid from the body. [2]

2. Certain foods and drugs may elevate uric acid levels and lead to gout attacks. These include the following:

- Foods such as shellfish and red meats, anchovies, herring, sardines.
- Organ meats – kidney, liver, heart, brain, gravies, sweetbreads, broths
- Beer (Due to high level of Guanosine), Spirits > Wine for developing gout as a disease (all forms of alcohol trigger gout flares in patients with established gout).
- Sodas and energy drinks sweetened with high fructose corn syrup (Fructose causes increased nucleotide turnover and hence more uric acid production and also inhibits uric acid excretion). [2]
- Certain medications

- low-dose aspirin (At doses of less than 2.5g/day, salicylates cause retention of uric acid by blocking the tubular secretion of uric acid), certain diuretics such as hydrochlorothiazide [3] (Dose dependent and needs frequent dose assessment)
- Immuno-suppressants used in organ transplants such as Cyclosporine (renal toxicity) and Tacrolimus.
- Theophylline used by Asthmatic patients (Theophylline increases the plasma concentrations of purine bases like Uric acid, Hypoxanthine and Xanthine).
- Beta blockers and Angiotensin receptor blockers (ARB's) other than Losartan can increase serum uric acid levels.
- Anti-hypertensive agents like Captopril. (It was noticed that Losartan decreased uric acid levels in serum).
- Cytotoxic drugs like Anthracyclines and Doxorubicin (Increased cell turnover, renal damage, Tumor lysis syndrome).
- Nicotinic acid used to treat Dyslipidemia.
- Smoking

(1) Genetics: Partly genetic.

Few these disorders, like Medullary cystic kidney disease and HGPRTase deficiency as seen in Lesch-Nyhan syndrome are complicated by gout. [4]

(2) Medical conditions: Medical conditions like renal failure, Diabetes, Syndrome X, Polycythemia, Lead poisoning and Psoriasis.

Increased uric acid levels in the blood leads to Mono-sodium urate crystals in and around the joints. These crystals incite inflammatory response, leading to severe, painful gout attacks and chronic arthritis.[5]

EPIDEMIOLOGY

- Men: most often affecting middle –aged(40 – 50 yrs)
- Women: usually postmenopausal and elderly (< 15% prior to menopause; seen mostly in individuals with a strong family history of gout.)
- Prevalence influenced by factors such as hormonal, geographic, racial, genetic, dietary, background conditions:

- Males > Females (7:1 - 9:1) because Estrogen is uricosuric.
- Hypertension
- Renal transplant (2 – 13%) due to use of Immuno-modulators.

Pathophysiology

Gout is a disorder of purine metabolism, characterized by the formation of uric acid which crystallizes in the form of monosodium urate, precipitating in joints, over tendons, and in the surrounding tissues. These crystals then incite an acute inflammatory reaction. Uric acid can crystallize at normal blood levels as well as high levels, which is more common. Other factors believed that incite Acute gouty reaction include rapid changes in uric acid levels and Acidosis (Renal Failure). [6]

Signs and symptoms

The joints farther away from the body core have lower temperatures which allow the Mono-sodium urate crystals to precipitate faster. The metatarso-phalangeal joint (Podagra) of the first toe is often involved (80-90% cases), but tarsal joints, ankles, and knees are also commonly affected. Inflamed Heberden's or Bouchard's nodes may be an earliest sign of gouty arthritis

Joint pain usually begins over 2–4 hours and during the night which wakes the patient from sleep which is because of lower body temperatures at night. Very rarely it is also seen involving the Temperomandibular Joint also, Accompanying features like fever and fatigue can be present. [7] Joints rapidly become warm, red, and tender, often mimics cellulitis.

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Long-standing hyperuricemia can result in peri-articular tophaceous deposits causing joint erosion and can enlarge and burst leading to white chalky discharge which can lead to chronic non-healing ulcers complicated by secondary infection.

High uric acid levels in the blood can lead to crystal deposition in renal tissue which can cause urate nephropathy and subsequent renal failure.

MSU crystals can accumulate in bursae causing Tendoachillis bursitis, tophaceous deposits over the fingers and ears can cause palpable subcutaneous nodules.[8)]

HYPERURICEMIA vs GOUT

- **Hyperuricemia is**
- serum urate concentration exceeds urate solubility (~6.8 mg/dL)
- Caused by overproduction and/or under excretion of uric acid
- No gout without crystal deposition

- Gout is deposition of monosodium urate crystals in joints and tissues. [(9)]

DIAGNOSIS: the diagnosis of gout should be confirmed by needle aspiration of acutely or chronically involved joints or tophaceous deposits

Synovial fluid

Identification of needle shaped monosodium urate crystal both in aspirated synovial fluid or a tophus by Strong negative birefringence from blue to yellow color as seen in Light microscope. Collection of synovial fluid in LHT (Lithium Heparin Tube) to prevent dissolution of urate crystals.[(10)] Synovial fluid cell counts are elevated from 2000 to 60,000/μL

Blood tests

Hyperuricemia is defined as a plasma urate level > 6.8 mg/dl. In few cases of Gout it can be within normal range as well.

Raised level of WBC count, electrolytes and ESR may be seen. However, both the white blood cells and ESR may be elevated due to gout in the absence of infection.[(11)]

X-Rays:

There occurs articular cartilage damage owing to pannus. Cystic changes, well-defined erosions with sclerotic margins (often with overhanging bony edges), and soft tissue masses are characteristic radiographic features.

Management of gout should start from the very basic issues:

1. Intake of plenty of fluid 3-4 liter per day in the form of water, fresh fruit juice, tea & coffee, skimmed milk, yoghurt, soya beans and vegetable sources of proteins should be encouraged.

2. Patient who are diabetic or have dyslipidemia should restrict the consumption of saturated fat and sugar.

3. Avoid thiazide diuretics, aspirin or pyrizinamide in a patient on ATD regimen.

4. Patient should attempt for Gradual weight reduction and not crash diet and over exercise.

5. Reduce high protein diet, red meat, fish eggs and alcohol/beer, intake.
6. Avoid smoking.
7. During acute attack Xanthine oxidase inhibitors like Allopurinol, Uricosuric drugs like Probenicid and Sulphinpyrazone are best avoided as, they may prolong the attacks or even cause renal complications.
8. Alkalinize the urine by sodium bicarbonate.

Drugs during an acute attack:

1. Colchicines, One to two 0.6-mg tablets can be given every 6–8 h over several days with subsequent tapering. This is generally better tolerated than the formerly advised hourly regimen. The drug should be stop immediately at first sign of toxicity in the form of nausea, vomiting and diarrhea.

2. The most effective NSAIDs are any of those with a short half-life and include Indomethacin, 25–50 mg thrice a day; ibuprofen, 800 mg thrice a day; or Diclofenac, 50 mg tid.

3. Oral glucocorticoids such as prednisone, 30–50 mg/d as the initial dose and gradually tapered with the resolution of the attack can be effective in poly-articular gout.

4. For single or poly-articular gout, intra-articular triamcinolone acetonide, 20–40 mg, or methylprednisolone, 25–50 mg, have been effective and well tolerated.

5. Adrenocorticotropic hormone (ACTH) as an intramuscular injection of 40–80 IU in a single dose or every 12 h for 1– 2 days can be effective in patients with refractory gout or in those with a contraindication for using NSAIDs or Colchicine.

Hypouricemic Therapy:

Initiates when:

The number of acute attacks frequent (cost effective after two attacks)

Serum uric acid levels [progression is more rapid in patients with serum uric acid (>9.0 mg/dL)]

Patient's willingness to commit to lifelong therapy

Presence of uric acid stones

b Uricosuric : These help in excretion of uric acid like

Probenecid started at a dosage of 250 mg twice daily and increased gradually as needed up to 3 g .

Sulfinpyrazone given in the dose of 100-200mg per day.

Xanthine Oxidase inhibitors: This block the conversion of hypoxanthine xanthine to and subsequent uric acid.

Allopurinol has been used for a long time , can be given in a single morning dose, 100–300 mg initially and increasing up to 800 mg if needed.. So as to achieve a target of serum urate level of < 360 umol /L the dose adjustment should be based on Creatinine clearance. It is the drug of choice in patients with Cardiovascular diseases. It has side effect involving GI tract, rarely blood dyscrasias and hepatic damage hence it is mandatory to do regular blood count and liver function tests.

The advantage of new molecule Febuxostat has show better ef-

fects especially in tophi reduction and patient with mild to moderate renal dysfunction as it requires no dose adjustment. It is given in the dose of 40 to 80mg, 2-3 times per day orally. These drugs are also useful for management of chronic hyperuricemia. This molecule is linked with increased risk of Cardiovascular and Thrombo-embolic side effects. According to US FDA "Fatal and no fatal hepatic failure has been reported, LFT should be done as a base line before starting Febuxostat, when the ALT >3 times the normal range this drug is best avoided. [12] It should be stopped immediately if, signs of hypersensitivity reactions like anaphylactic shock or Stevens Johnson Syndrome is noted.

Allopurinol and Febuxostat should never be given simultaneously [13]

Asymptomatic Hyperuricemia does not require any treatment.

Myths and Truths of Gout

MYTHS	TRUTHS
Gout is a rare and un-complicated disease	Gout is 5 times more common than Rheumatoid arthritis. Prevalence of Gout has increased to about 60% in older adults. Gouty arthritis is associated with about 38% increased risk for cardiovascular disease related deaths and 55% increased risk for Coronary heart disease. [14]
In Gout, only 1st Metatarsal is involved.	1st metatarsal is the most commonly involved joint (75%), but knees (53%), ankles (51%), elbows (24%), shoulders (14%) etc. are also involved. [15]
Eggs and Diary products contain high purines, therefore should be restricted.	Eggs and Dairy products contain almost no purines or <13mg/100g. [29]
All sea food is good, they are even beneficial to the heart.	Most fish, shellfish, shrimps, mollusks and especially dried fish, contain Hypoxanthine as >505 of their total purines which is risky. Oily fish can be taken moderately as it does not elevate Serum uric acid and can decrease risk of heart disease. [29]
Meat is nutritious and beneficial.	All meat contains very high purines. Chicken liver, beef, pork and their gravies should be avoided. Chicken should be moderated. [29]
All alcohols and the same. It's the amount of alcohol and ethanol that matters.	Beer contains not only ethanol but also high levels of Guanine and also reduces the excretion of uric acid more than other alcohols. [30] Even moderate alcohol consumption (2 drinks/day for men and 1 drink/day for women) was associated with 41% increased risk of recurrent gouty attacks. [30]
Seasonings, small quantities are used during cooking, does it make a difference?	Several seasonings like beer-yeast and Chlorella contain high amount of purine and should be avoided. [30]
Mono-articular arthritis in a patient with established Gout is always Gout.	There should be a concern for Septic arthritis as Gouty arthritis and Septic arthritis and often co-occur. [16]
Gout is always mono-articular and can never be poly-articular.	Elderly Gout can often present as sub-acute and chronic poly-articular disease. Often mimicking Rheumatoid arthritis. [17]
If Serum Uric acid is normal in a setting of Acute arthritis, it is not Gout	Serum Uric acid has low sensitivity and specificity in the setting of Acute Gout. Two randomized clinical trials for Treatment of Gout showed that 14% patients had Serum Uric acid less than 6mg/dL during Acute Gout. [18]
NSAIDs are preferred in the treatment of Gout	Low dose Colchicine, NSAIDs, Oral corticosteroids and intra-articular steroids are all effective choices for Gout, Proper patient choosing criteria is necessary to find the best therapy. [19]
Urate lowering therapy (ULT) should be started in treatment of Acute Gout	ULTs like Allopurinol and Febuxostat should not be started during an attack of Acute Gout as they may cause rapid Uric acid level fluctuations which can precipitate a Gout flare. [20]
ULT should be stopped during Acute Gout attack	Stopping ULTs can suddenly increase Uric acid levels which can cause Gout to flare up.
Once diagnosis of Gout is established, only Allopurinol or Febuxostat can be chosen.	Allopurinol is considered First line ULT after considering Safety, Efficacy and Cost. Also preferred in Cardiovascular patients. To choose best medication, one must follow proper guidelines after considering co-morbid conditions like Hypertension, Diabetes, Dyslipidemia and Kidney disease. [21]
Febuxostat is newer and better alternative than Allopurinol.	Febuxostat is preferred ULT in patients with mild to moderate renal impairment as it requires no dose adjustments. [22]
Allopurinol 100mg is sufficient in all patients with Gout.	Allopurinol should be started with 100mg once daily and should be increased every 2-4 weeks if adequate Serum Uric acid level is not reached upto maximum permissible dose of 900mg. [23]
With Allopurinol, no dosage modifications are required in patients with renal impairment.	The dose of Allopurinol dosage should be started at smallest level and should be adjusted based on Creatinine clearance. [24]
Allopurinol + Febuxostat give faster results.	Allopurinol and Febuxostat should never be co-administered. [25]
Febuxostat is safer alternative to Allopurinol.	Febuxostat is linked with higher risk of cardiovascular thromboembolic events. [25]
Febuxostat does not cause Hypersensitivity reactions like Allopurinol.	Febuxostat can cause hypersensitivity reactions like Stevens Johnson syndrome and Acute Anaphylactic shock mostly during first month of treatment. [26]
Febuxostat is not associated with liver impairment.	According to U.S. FDA: Fatal and non-fatal hepatic failures have been reported in patients taking Febuxostat. LFT should be done as a baseline before starting Febuxostat. [27]
Asymptomatic hyperuricemia should be treated.	Guidelines do not recommend treatment of Asymptomatic hyperuricemia.
With diet and lifestyle changes alone, Serum uric acid levels can be lowered and Gout controlled.	Diet and Lifestyle changes have been implicated in the pathogenesis of Gout which needs to be addressed simultaneously but effective Urate lowering therapy is the mainstay of treatment of Gout. Lowering body weight in obesity can be attempted but crash dieting should be avoided. [28]

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Volume : 5 | Issue : 4 | April 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

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