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

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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). (3)
- 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 (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 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 mono-sodium 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.
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.

**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

**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. 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.

**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/beef, intake.
6. Avoid smoking.
7. During acute attack Xanthine oxidase inhibitors like Allopurinol, Uricosuric drugs like Probenecid and Sulphinpyrazone are best avoided as, they may prolong the attacks or even cause renal complications.
8. Alkalinate 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-
Urate lowering therapy (ULT) should be started in treatment of Acute Gout.

Stopping ULTs can suddenly increase Uric acid levels which can cause Gout to flare up. (20)

Once diagnosis of Gout is established, only Allopurinol or Febuxostat can be chosen.

Febuxostat is preferred ULT in patients with mild to moderate renal impairment as it requires no dose adjustments. (22)

Febuxostat is newer and better alternative than Allopurinol.

Febuxostat is linked with higher risk of cardiovascular thromboembolic events. (23)

Febuxostat does not 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. Losing body weight in obesity can be attempted but crash dieting should be avoided. (20)

References:

(1) Cutaneous deposition diseases. Part II Diane M. Touart, MC MAJ, USA Purnima Sau, MC COL, USA

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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)

First metatarsal is the most commonly involved joint (75%), but knees (53%), ankles (51%), elbows (24%), shoulders (14%) etc. are also involved. (11)

Eggs and Diary products contain high purines, therefore should be restricted.

Eggs and Diary products contain almost no purines or < 1.5mg/100g. (20)

Most fish, shellfish, shrimps, mollusks and especially dry fish, contain Hypoxanthine as >50% 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. (20)

All sea food is good, they are even beneficial to the heart.

Serum uric acid levels can cause Gout to occur.

All meat contains very high purines. Chicken liver, beef, pork and their gravies should be avoided. Chicken should be moderated. (20)

Beer contains not only ethanol but also high levels of Guanine and also reduces the excretion of uric acid more than other alcohols. (20)

Febuxostat give faster suppression of hyperuricemia.

Febuxostat can be treated.

Febuxostat is safe alternative to Allopurinol.

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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. (20)

Even moderate alcohol consumption (2 drinks/day for men and 1 drink/day for women) was associated with 41% increase in uric acid level fluctuations which can precipitate a Gout flare. (26)

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