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REVIEW ARTICLE

Pathophysiology, Clinical consequences, Epidemiology and Treatment of Hyperurecemic gout

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ABSTRACT

Hyperuricemia is a common metabolic disorder worldwide with an increased level of serum urate/ uric acid (UA) up to 6.8 mg/Dl. It is a precursor of gout, a rheumatic inflammatory disease characterized by the deposition of uric acid in the form of monosodium urate (MSU) crystals in joints. It may be due to under secretion or over production or both. MSU crystals stimulated a powerful inflammatory reaction resulted in acute pain in joints. There are various marketed drugs used for the treatment of hyperuricemia i.e. allopurinol and Febuxostat .globally the prevalence of hyperurecemic gout is increasing day by day, it is 138th ranked factor of disability.it is more prevalent in male as compared to female and more present in developed countries than underdeveloped countries .it can be minimize by life style modification. Present attempt has been made to summarize the pathophysiology, clinical consequence, epidemiology and conventional treatment of hyperurecemic gout.

HYPERURICEMIA

The term denotes the increased level of uric acid in blood known as hyperuricemia. It is a biochemical abnormality higher level of serum uric acid greater than 7.00mg/dl. Serum uric acid level increases as a result of increased production or decreased secretion or both. Uric acid is a chemical substance that is produced by metabolic end product of the purines. Then it dissolves into the blood and filtrate out through the kidney. If kidneys don't filter out the uric acid

it level becomes higher and leads to a medical condition known as hyperuricemia. Many factors are responsible for this condition .It is the precursor of the gout, metabolic syndrome, joint damage, pain, endothelial dysfunction and many other medical conditions.it may be symptomatic or asymptomatic [1-3].

CAUSES OF HYPERURICEMIA

Under secretion of uric acid

- Idiopathic hyperuricemia
- Renal failure
- Impaired function of kidney
- Nephropathy
- Nephrolithiasis
- Glomerulonephritis
- Hypertension
- Metabolic acidosis

Overproduction of uric acid

- Purine rich diet
- Immune suppressant drugs
- Diuretic medications
- Alcohol consumption
- Deficiency of vitamin B3
- Psoriasis
- Tumor lysis syndrome
- During the course of radiotherapy and chemotherapy

Both overproduction and underproduction

- Glucose 6-phosphate deficiency
- Hypo perfusion of tissues
- Abuse of drugs
- Hepatocyte nuclear factor-1β gene mutation [4-8].

RISK FACTORS OF GOUT

There are many factors which exaggerate the development of gout. By preventing these factors risk of development of gout can be minimized [9, 10] . These are followings:

Diet

Protenious diet is the risk factor for the development of the gout. Diet rich in purines, high dens portentous food including sea food and meat are the risk factor for gout. They increase the production of much uric acid resulting gout. Consumption of alcohol, beers also causes gout. Higher level of fructose promotes the production of uric acid. Intake of vitamin C, dairy products and coffee reduce the risk of gout [11-13] .

Obesity

A person ranging BMI greater than 25 are at higher risk level of gout. Body produce more uric acid and kidney are enable to excrete up to an optimum limit. It's harder for kidney to eliminate a uric acid level. So it is advised to reduce the weight so that risk can be minimized [14].

Medication

There are many medications that increase the risk of development of gout. Certain medications including beta blockers, aspirin, angiotensin and immune suppressant agents are liable to increases uric acid level and risk factor for gout. A literature was published to document the effect of diuretics on development of gout. Results show that diuretic impact a significant role in the development of gout.

Family history

Positive family history correlates with the development of gout. If one of member of your blood relation is suffering with gout it is more likely a risk factor of gout.

Gender and sex

Gender is also important while we are discussing risk factors of gout .men at the age of 30-50years are at higher risk of gout than women. Women after menopause are more liable to develop gout, so the level of uric acid increases.

Trauma and surgery

Recent surgical procedure or traumatic situations may also tend at higher level of risk of gout.

Metabolic syndrome

Medical situations such as diabetes, hypertension, and obesity are at higher risk of gout [9].

GOUT

Impaired metabolism of purines that don't proceed uric acid to excrete out through kidney leads to accumulation of uric acid in joints and synovial fluid that causes pain and inflammation condition is labeled as gout [15]. Uric acid may accumulate into tissues near joints or cartilage. Hyperuricemia is the precursor of the gouty arthritis. Initially it involves one joint known as monoarticular arthritis and after that all joints became involved polyarticular arthritis [16] . Gout is known as from the times of Egyptian. it affects 1-2% population. The prevalence of gout is increasing day by day. The level of uric acid is directly proptional to the occurrence of gout. it is the leading cause of the morbidity.it is also known as the rich man disease [17, 18].Polycystic kidney disease, renal failure, consumption of alcohol immune suppressing, antidiuretic drugs and high content protein food are at higher risk of gout. Genetically the deficiency of hypoxanthine-guanine phosphoribosyl transferase can lead to the gout. Mutation in the SLC2A9 and SLC22A12 gene follows hyperuricemia. Medical conditions such as obesity, insulin resistance, tumor, and polycythemia are the risk factors of the gout [19-21].

Pathophysiology of gout

Hyperuricemia is the leading cause of the gout. However it is not obvious that gout is definitely from hyperuricemia. It may be due to other etiological factors. It is believed that gout is more prevalent in individuals having elevated serum uric acid level.

Uric acid is a weak acid that is formed end product in our body as a result of purine metabolism then it is secreted through excretory and digestive system of our body. 1/3rd part of uric acid is breakdown in gut through bacteria while 2/3rd part is excreted through kidney.

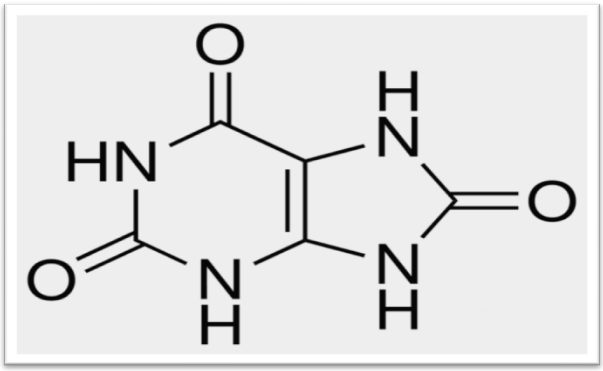

Figure 1: Chemical formula of uric acid

The intermediate of purine nucleotides metabolism are hypoxanthine and xanthine. Xanthine oxidase is an oxidoreductase that generate the reactive oxygen species and catabolize the [22]. Overproduction of uric acid due to greater intake of purine rich diet and less excretion through body or combination of both causes hyperuricemia .

Clinical picture of gout

Gout is a common metabolic abnormality usually exhibits no symptoms in most of the cases it asymptomatic however the following stages are in course of gout.

- Asymptomatic hyperurecemic gout

- Acute gouty arthritis
- Intercritical gout
- Chronic tophaceous gout
- Chronic articular gout

Gout is more prevalent in male at puberty and in female after menopause. The attack is sudden and it usually involve single joint (monoarticular). There is localized pain, erythema, heat and fever. Mostly it involves metatarsophalangeal joint. Acute gouty arthritis is a painful situation usually occurs as a result of elevated level of uric acid in the blood and monourate sodium crystal accumulated and causes inflammation of joints. It may involve knee, ankle wrist and fingers. Mostly it resolves in 5-7 days. If it is not resolved then recurrent episode of gout occurs and becomes chronic .when there is loss of joint space and erosion of juxtaarticular bone due to monourate sodium crystal (MUS). In chronic stage it also exhibit renal complaints and embolism of tophaceous crystals occurs. It is documented that 20% of patients with chronic gout die due to renal failure [23-25].

Complications

- Formation of tophi (crystals of uric acid accumulated under the skin and give lumpy appearance known as tophi. It may appear on toes, ears, forearms, elbows etc.)
- Renal calculi
- Renal failure
- Anxiety
- Depression
- Joint deformity
- Life style disability (walking and sleeping difficulty)

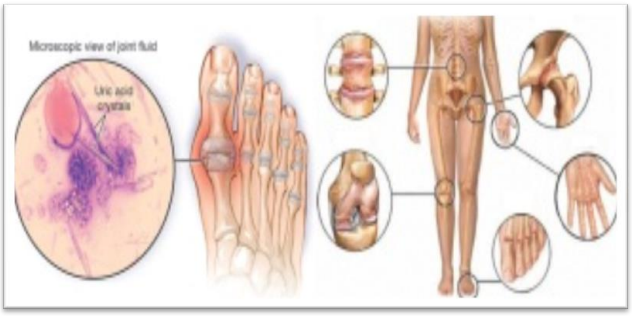

Figure 2: Sign and symptoms of gout

Diagnosis

- Blood test (uric acid assay)
- X-rays imaging technique (to estimate the inflammation of joint)
- Joint fluid test (to investigate the presence of monourate sodium crystal)
- Dual energy CT scan (to estimate presence of tophi in joints)
- Ultrasonography (to detect presence of urate crystal in joints)

Conventional management of gout

Xanthine oxidase (XOD) is an oxidoreductase enzyme which catalyzes the hypoxanthine in to xanthine and finally into uric acid. The therapeutic approach for the treatment of the gout is the inhibition of the xanthine oxidase. Xanthine oxidase inhibitor is the drug of the choice for treating hyperuricemia. Other drugs such as Uricosuric drugs can be used in treating gout [26, 27]. Therefore there is the need of the time to introduce and evaluate the new hyperuricemia agent with minimal adverse effects.

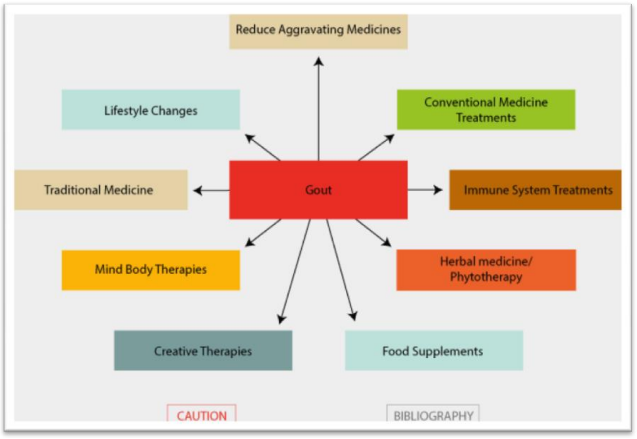

Figure 3: Management of gout

Life style modification

Gout is the leading cause of morbidity and mortality. The morbidity of gout can be minimized by life style modification such as limiting the risk factors such as obesity, purine rich diet, certain medication i.e. diuretics, consumption of alcohol, hypertension, diabetes mellitus [10, 28] .

Allopurinol

Allopurinol is used as the first line treatment in treatment of hyperuricemia. Mechanism of action of the allopurinol is to block the xanthine oxidase and lower the serum uric acid level. Xanthine oxidase is an oxidoreductase that catalyzes the hypoxanthine into xanthine and finally into uric acid. The dose of allopurinol for patients with normal renal function is 100mg dose/day with 0.5mg NSAID (non-steroidal anti-inflammatory drug). The dose of allopurinol can be increased until the level of uric acid reaches normal. The dose can be increased as 400-900mg/day depending upon the condition of patient and level of serum urate. Allopurinol causes severe hypersensitivity reaction and sometime causes the Steven Johnson syndrome. Allopurinol also interact with others drugs such as azathioprine and causes bone marrow suppression [11, 29-31].

Febuxostat

Febuxostat is more safe and effective than Allopurinol in reducing serum urate level. It is a safer drug of non-purine inhibitor of xanthine oxidase. A study was conducted to compare the allopurinol with Febuxostat. Results revealed that Febuxostat is more effective in reducing uric acid level than allopurinol [32, 33].

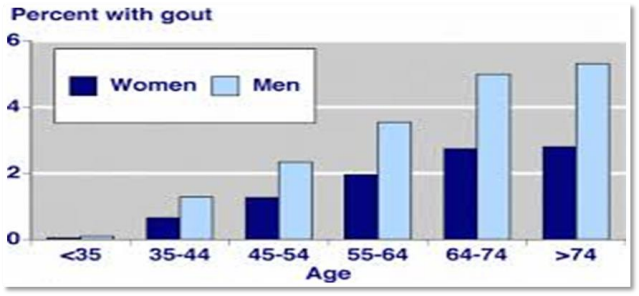

Figure 4: Prevelance of gout in men and women in different age group

Other therapeutic agents

Other therapeutic agents such as Uricosuric drugs such as sulfipyrazone and benzbromarone can be used alternative approach to hyperuricemia in cases where there existence of hypersensitivity reaction, intolerance to allopurinol and renal failure are present [34-37] .

Prevalence of gout and hyperuricemia

The prevalence of gout in US population is 3.9% in year of 2007-2008 among which male were more inclined to hyperuricemia i.e. 5.9%and female were 2.0% [38]. The prevalence of gout is increasing day by day globally [39]. In the developed countries the incidence of gout is greater than the underdeveloped countries and some ethnic group are more prone to be predisposition of gout [40]. The prevalence of hyperuricemia in china is lower than the rest of world and it is only endemic where there obesity is present at background [41]. Gout and hyperuricemia is more liable in male than female. Male to female ratio for hyperuricemia and gout

is 2:1, 34:1 respectively [42]. Worldwide prevalence of gout is 0.08%. It is a leading cause of morbidity and mortality. It is ranked as 138th number as a disability factor and impact an economic burden [43]. in comparison with world prevalence of gout is highest in Australia and it is comparable with new Zealand [44]. In Karachi, Pakistan the prevalence of gout is more in male as compared to females in adult ages and in female it occurs after menopause[45].

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