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Review Article

UNDERSTANDING GOUT BEYOND DOUBT

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ABSTRACT

Life is all about movements and activities. Our entire livelihood and existence comes into trouble, we become immobile and inactive due to joint pains and swelling. Gout is one such condition, which affects an individual's life. Gout is a type of arthritis that occurs, when too much uric acid builds up in the body, causing deposition of urate crystals in the joints. It is accompanied by excruciating, unexpected, burning pain, swelling and inflammation leading to complete immobility of the joints. Gout can be hereditary. Excessive intake of certain types of food, alcohol, infection, physical or emotional stress, or the use of certain drugs can lead to the development of gout symptoms. Gout occurs commonly in men (over 40 years of age) affecting their toes, but can appear in other parts of the body as well. It affects women too, especially after menopause. Low-grade fever may be present during gout attack. The crystals formed inside the joints cause intense and debilitating pain. The inflammation of the tissues around the joint causes the skin to become swollen, tender and sore, to even a slight touch. The lightest sheet draping over the affected area could cause extreme pain. It is commonly treated with anti- inflammatory medicines or corticosteroid drugs. The patients always seek for fast and quick relief, so that they can resume their daily routine. The present review article focuses on the causes, pathophysiology and various treatment options available to the gout patient.

Keywords: Gout, Hyperuricaemia, Tophus, Uric acid, Joints

INTRODUCTION

Life is all about movements and activities. Our entire livelihood and existence comes into trouble, we become immobile and inactive due to joint pains and swelling. Gout is one such condition, which affects an individual's life. The word gout was initially used by Randholphus of Bocking, around 1200 AD. The term 'gout', is derived from Latin word 'gutta' and French word gote, both meaning a drop of liquid. Several hundred years ago gout was thought to be caused by drops of viscous humors that seeped from blood into the joints. It has been called as the 'disease of Kings[1], because of its association with the kind of over-indulgence in food and wine, which only the rich and powerful could afford. Gout is a chronic and progressive disease, which results from an overload of uric acid in the body, which is actually a waste product[2]. This overload of uric acid leads to the formation of tiny crystals of urate that deposit in the tissues of the body, especially the joints. These deposits cause recurring attacks of joint inflammation (arthritis). Acute and chronic forms of gout are recognized. Acute gout is characterized by rapid onset of excruciating pain and swelling linked with redness of the affected joint. In the initial attacks, the onset is in the first meta-tarsophalangeal joint (MTP), and this joint is affected in some 90 % of patients with gout. A Chronic form of gout is associated with deposition of crystals in soft tissues, joints, bones and tendons[3]. They cause erosion and destruction of the bone, leading to crippling. The patients, who develop chronic gouts, are usually those, whose hyper- uricaemia is not controlled. Primary gout is related to under excretion or overproduction of uric acid[1]. Secondary gout is caused due to myeloproliferative diseases or their treatment, therapeutic regimens producing hyperuricaemia, renal failure, renal tubular disorders, lead poisoning, hyper proliferative skin disorders, enzymatic defects etc. (e.g., deficient hypoxanthine-guanine phosphoribosyl transferase, and glycogen storage diseases). It is a rheumatic syndrome caused by an inflammatory response to the formation of monosodium urate monohydrate crystals, which develop secondary to hyperuricaemia (elevated blood uric acid levels)[1,3]. But some people may only develop hyperuricaemia without having manifestations of gout, such as arthritis or kidney problems. It is referred to as asymptomatic hyperuricaemia, which is considered as a precursor state to the development of gout[2]. Gout affects quality of life of the sufferers during the episodic attacks and its potential for chronic arthritis. This disease is very painful and becomes a major obstacle in professional or social life, because of inflammation and tremendous pain.

History

Gout is one of the oldest diseases in the medical literature[4]. Many authors have written about gout since the time of the Greeks. Its association with a diet rich in meat and alcohol gained it the sobriquet, "the king of diseases and the disease of kings"[1]. However, among the abstinent was John Milton. He lived a life of self-discipline and yet, to his despair, he suffered from what commonly was regarded as just punishment of the dissolute. Antonie Leeuwenhoek described the microscopic appearance of uric acid crystals in 1679. In 1683, Thomas Sydenham an English physician described its occurrence in the early hours of the morning, and its predilection for older males. In 1848, Sir Alfred Garrod linked gout with hyper-uricaemia. The discovery of elevated serum uric acid levels in gouty patients is normally credited to Garrod in 1859. But, the pathophysiology of acute gouty arthritis was not described fully until 1962[5]. Since then, gout has been associated with a large number of different auto-immune and metabolic disorders. The first written description of gout dates back to 2600 BC, when Egyptians noted the gouty arthritis of the big toe. Around 400 BC, the Greek physician, Hippocrates, also commented on gout[1]. Aulus Cornelius Celsus (30 AD) described its linkage with alcohol, kidney problems and menopausal women.

Prevalence

Gout has a global distribution. The worldwide occurrence of gout is 0.3 %, but variations are seen country wise. According to the National Institute of Arthritis and Musculo-Skeletal Disease, gout has been a serious medical condition prevailing in almost 275 out of every 100,000 people in the world. According to the Centers for Disease Control and Prevention (CDCP), gout affects approximately 3 million people in the United States each year. The incidence of gout is 3.11 per 1000 person in African Americans and 1.82 per 1000 person in whites. This difference is because of the excessive risk of hypertension. In contrast, clinically recognized gout is extremely rare among blacks living in Africa. According to studies the incidence of gout was low among hypertensive women. But hypertensive men are four times more likely to develop this condition. Approximately 18 % of people who suffer from this disease have a hereditary linkage. Environmental, dietary, and genetic factors also influence its prevalence influences. There is some evidence from different parts of the world that gout occurs more frequently in the spring season in the northern hemisphere[6]. In England, gout affects 16.4 of every 1000 men and 2.9 of every 1000 women. In the Maori people of New Zealand, 10.3 % of men and 4.3 % of women are affected. Gout has a male predominance. In men, uric acid levels rise at puberty, and the peak age of onset of gout in men is in late 40s to 60s. But due to lifestyle and genetic linkage onset may occur in men in their early 20s. In women, uric acid levels rise at menopause and peak age of onset in women is in the fifth to eighth decade of life[5]. Cyclosporine A can cause an accelerated form of gout, even in premenopausal women, that particularly if the patient is also receiving diuretics. The National Health and Nutrition Examination Survey (2007-2008) estimated a new prevalence for gout and hyper uricaemia. Gout rates were reported as 5.9 % among men and 2 % among women. Whereas prevalence rate of hyperuricaemia was noted as 21.2 % for men and 21.6 % for women. This difference is largely a consequence of age, because estrogenic hormones have a mild uricosuric effect[7]. It is rare in children and young adults but affects 1.3 % of elderly patients. The predominant age range is 30-60 years. The higher prevalence of tophaceous gout in elderly persons may also reflect an increased prevalence of diabetes, high rates of diuretic treatment for hypertension for e.g. thiazides and congestive heart failure[5], and the use of low-dose of aspirin. Earlier onset of gout occurs in patients with renal insufficiency or a genetic abnormality of purine metabolism (e.g. hypoxanthine-guanine phosphoribosyl transferase deficiency, phosphoribosylpyrophosphate synthetase super activity).

Causes

Knowing the essential causes of gout can help in proper diagnosis and eradication of this disease from the roots. There are several individual reasons behind causes of gout, and it is highly important to determine each factor individually and prescribe appropriate treatment for each cause.

Gender

It plays a key role. It has been found that men are more likely to fall victims of gout syndrome much earlier and in more numbers as compared to women. Triggering factors for acute attack remain same for both men and women. Individual gout flares are often triggered by acute increases or decreases in urate levels that may lead to the production, exposure, or shedding of crystals that are not coated with Apo B or Apo E.

Lifestyle

Certain conditions related to nutrition and lifestyle include Obesity[8], emotional stress, frequent episodes of dehydration, injury to a joint, very low-calorie diet and moderate to heavy alcohol ingestion (particularly beer, which is rich in purines). Alcohol can reduce the excretion of uric acid by the kidneys into urine, causing an increase of uric acid level in the body. Beer confers a larger increase than liquor, whereas moderate wine drinking does not increase serum uric acid levels. A higher intake of added sugars or sweetened drinks leads to higher blood levels of uric acid. Researchers have reported, in general, that meat or seafood consumption (high-purine foods) increases the risk of gout attacks[1], while dairy food consumption seemed to reduce the risk[9].

Medication

Medicines that may increase uric acid concentration include regular use of aspirin or niacin, diuretics, chemotherapeutic agents, immunosuppressants such as cyclosporine and medicines that are used to treat tuberculosis[5].

Medical Conditions

Major illness, infection or certain medical conditions like rapid weight loss, chronic kidney disease, high blood pressure, hypothyroidism and hemorrhage may enhance the risk of gout. Conditions that cause an abnormal rapid turnover of cells, such as psoriasis, multiple myeloma, hemolytic anemia, or tumors may lead to gout. Lead poisoning or Chronic low level lead exposure may inhibit urate excretion[10]. High glycerides levels are also important risk factors. Surgery is another cause of gout.

Genetics

Genetic studies have found that variants of Glucose transporter 9 (GLUT9) and ATP-binding cassette sub-family G member 2 (ABCG2) were associated with urate levels[11]. According to the National Institute of Arthritis and Musculoskeletal and Skin Diseases, approximately 18 % of people, who develop gout, have a family history of gout. Inherited genes from the family contribute to almost 60 % variation in the level of uric acid in the blood. People with Kelley-Seegmiller syndrome or Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyl transferase deficiency), von Gierke disease (glucose-6-phosphatase deficiency) have a partial or complete deficiency in an enzyme that helps to control uric acid levels. Absence of enzyme uricase also results in high uric acid levels. Persons with Fructose 1-phosphate aldolase deficiency, PP-ribose-P synthetase variants, familial juvenile hyperuricemic nephropathy[5] and medullary cystic kidney disease[5] show symptoms of gout. Thus, poor living habits and lifestyle conditions are responsible for causing gout disease.

Pathophysiology of Gout

Arthritis is of three types, *viz*. rheumatoid arthritis, osteoarthritis and gouty arthritis. Gout is very painful and leads to temporary or permanent disability. The biological precursor to gout is elevated serum uric acid levels (i.e., hyper uricaemia)[2]. At beginning stage, it generally affects one or two joints. But later on, it progressively spreads across various joints such as toe, ankle, knee, wrist, elbow or fingers. Uric acid is the metabolic product of RNA and DNA.

It is naturally formed in the body after consumption of certain food items that are rich in proteins, purines and fats. Usually uric acid is flushed away with urine in the normal course of the body. But, when the body fails to metabolize high protein and purine intake properly, it leads to increased levels of uric acid. Sometimes, due to kidney malfunctioning, such excessive uric acid cannot be removed from the body and gets deposited in the joints and tissues of the body. Excess deposition of uric acid results in the formation of chalky-white accumulations known as tophi. They are easily visible in joints of a finger and other extremities of the body such as nose, ears or toes[12]. When uric acid crystals come into contact with white blood cells, they cause extreme pain, redness and hot inflammation in the joints. When uric acid levels are high in the body they get precipitated in the kidney forming kidney stones. Uric acid stones (white or orange in color) are formed when urine has a low pH (very acidic). Micro tophi of urate crystals (highly negatively charged and reactive) are normally coated with serum proteins (apolipo protein Apo E or Apo B)[4]. This physically inhibits the binding of the urate crystals to cell receptors. A gout attack may be triggered by either a release of uncoated crystals (e.g. due to partial dissolution of a microtophus caused by changing serum urate levels) or precipitation of crystals in a supersaturated microenvironment (e.g. release of urate due to cellular damage). These naked urate crystals interact with cell receptors of local dendritic cells and macrophages, resulting into the activation of the innate immune system.

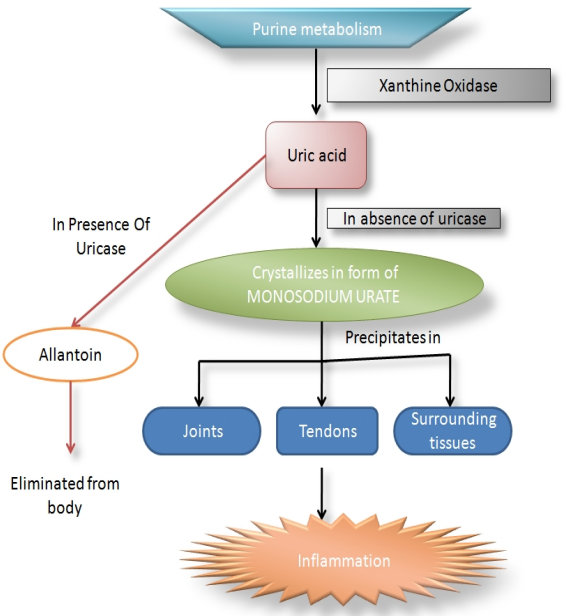

Figure 1: Pathophysiology of Gout

This interaction may be enhanced by immunoglobulin G (IgG) binding[13]. Triggering of the receptors {including Toll-like receptors (TLR)}[14], NALP3 inflammasomes[15], and the receptors expressed on myeloid cells (TREMs)) by MSU (monosodium urate), results in the production of interleukin (IL)–1. This in turn initiates the production cascade of pro-inflammatory cytokines, including IL-6, IL-8, neutrophil chemotactic factors, and tumor necrosis factor (TNF)–alpha[16]. Neutrophil phagocytosis leads to another burst of inflammatory mediator production. Subsidence of an acute gout attack is due to multiple mechanisms, including the clearance of damaged neutrophils, recoating of urate crystals, and the production of anti-inflammatory cytokines including, IL-1RA, IL-10, and transforming growth factor (TGF)–beta[17]. All this ultimately causes intense pain, redness and swelling around the joint area.

Symptoms

Gout usually develops after a number of years of buildup of uric acid crystals in the joints and surrounding tissues[1]. Signs and symptoms of gout are usually acute. But in some cases the individual doesn't feel any signs or symptoms, thus resulting into chronic gout. Gout might also appear after an illness or surgery. A significant proportion of patients experience them at night due to low body temperature at that time[5]. But these symptoms disappear within 5 - 10 days and reappear later on. In later attacks, lumps (called tophi[12]) are visible just under the skin in the outer ears, hands, feet, elbows, or knees and also present in some areas such as in the vocal cords or around the spinal cord. Tophi are not much painful. The patients may experience pain in ankles, hands, fingers, elbows, wrists, knees or feet. More commonly the base of the big toe is affected (podagra). The affected area becomes warm/hot, red/ purplish and stiff (Figure 2). Tenderness is so intense that even a bed sheet touching the skin over the affected joint can be unbearable. Tingling sensation is felt in the affected areas. But, sometimes the joint area may become numb due to the swelling and inflammation, and it become difficult to move that particular body part.

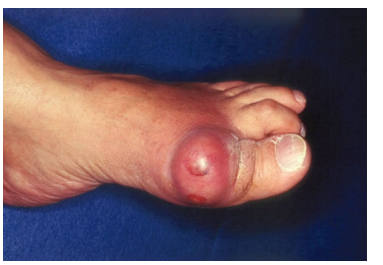

Figure 2: Podagra in elderly patient

These acute symptoms of gout ultimately lead to permanent disability in patients. The fluid sacs that cushion tissues (bursae) may get inflamed leading to bursitis. When this occurs in the elbow, it is called olcranon bursitis, while in the knee, it is known as prepatellar bursitis. The skin around the affected area may be itchy and peel off after the subsidence of gout attack. Some patients have an elevated temperature (102°F) with or without chills. This is generally caused due to the unbearable pain and imbalance of metabolism in the body.

Stages of Gout

There are three stages of gout[1]. Many people never experience the third stage.

First Stage (Asymptomatic hyper uricaemia)

The uric acid level in the blood may be higher than normal, but there are no symptoms of gout. Some people might have kidney stones before the first attack of gout (see Table 1).

Second Stage (Acute intermittent gout)

Episodes of acute gouty arthritis are separated by periods of no symptoms. Uric acid crystals begin to form in the synovial

fluid. The big toe is the most common site for the gout attack. Later on, it may develop in other joints such as knee, ankle, foot, wrist, and fingers. The affected joint and surrounding tissues feel normal in a few days. But symptoms often reappear within 2 years. For many individuals reappearance of gout attack is progressively shorter. Later attacks may be more severe, last longer, and involve more than one joint.

Third Stage (Chronic tophaceous gout)

If gout symptoms remain untreated for several years that condition is called chronic gout, affecting many joints. Sufficient uric acid crystals accumulate in the body to form tophi. These crystals are usually firm and movable, when deposited under the skin surface. The overlying skin is generally thin and red. Tophi that are very near the skin may appear cream-colored or yellow. At first, tophi are usually found on or near the elbow, over the fingers and toes, or on the outer edge of the ear. If the condition progresses without treatment, tophi may form in the cartilage of the external ear or in the tissues around the joint (bursae, ligaments, and tendons), resulting in pain, swelling, redness and warmth (inflammation). Progressive crippling and destruction of cartilage and bone also occurs. This stage of gout is commonly confused with osteoarthritis.

Diagnosis

The examinations and tests that are helpful in diagnosis and treatment of gout include medical history, physical examination and tests to measure levels of uric acid in blood and urine. Arthrocentesis is the most reliable test for diagnosing gout and is performed under local anesthesia. In this test, synovial fluid is aspirated from affected joint using syringe and analyzed under a microscope for presence of uric acid crystals. Blood uric acid levels are measured, when fluid cannot be aspirated easily from the affected joint. The blood test for uric acid helps in detecting kidney stones, efficacy of anti-gout medicines and side effects of chemotherapeutic agents. Uric acid blood levels vary on daily basis. The level is usually higher in the morning and lower in the evening. The uric acid urine test measures the amount of uric acid in a sample of urine collected over 24 hours. It is not necessary to restrict fluids or foods before the test. One must inform the doctor about all the non-prescription and prescription medicines one is taking and about alcohol drinking. Having a high uric acid level does not mean that you have gout. Uric acid crystals sometimes form in joints even at levels less than 7 mg/dL, especially in men. Women generally have slightly lower uric acid levels than men. To alleviate attacks of gouty arthritis and remove uric acid crystals from synovial fluid, serum uric acid has to be kept below 6 mg/dL (360 µmol/L)[2]. Normal level of uric acid in urine sample of 24 h is 250-750 mg or 1.5-4.4 mmol.

Table 1: Normal Uric acid levels in Blood

Men	3.4-7.0 mg/dL	202-416 µmol/L
Women	2.4-6.0 mg/dL	143-357 µmol/L
Children	2.0-5.5 mg/dL	119-327 µmol/L

Erythrocyte sedimentation rate (ESR) and Plain film radiography may be used to evaluate gout. Ultrasound and CT scanning can be used to study the effects of gout in areas that are hard to visualize with plain-film radiography. X-rays of extremities are sometimes useful in the late stages of the disease.

Drug Therapy

Treatment of gout includes drug therapy a well as non- drug therapy (steps that one can take at home to prevent future attacks). Body constitution, reaction to medicines and age are certain factors that must be kept in mind while treating the sufferers of gout. Ideally, the blood uric acid level should be below 6.0 mg/dL. This level of uric acid is referred to as the "target level" or "goal" of therapy.

Initial treatment: Pain, swelling, redness, and warmth of the joints represent the acute symptoms of gout. Initially, ibuprofen, naproxen, or indomethacin, are some non-steroidal anti-inflammatory drugs (NSAIDs) that are prescribed. In addition to NSAIDs, colchicine and corticosteroids are also prescribed. Colchicine and Oral corticosteroid (such as prednisone) are usually reserved for patients in whom NSAIDs are contraindicated and for resistant cases of gout respectively.

To prevent recurrent attacks

To prevent recurrent attacks, medicines that reduce the levels of uric acid in the blood and those, which reduce the risk of future attacks, are advocated. Uricosuric agents are used for such purpose. Drugs called xanthine oxidase inhibitors such as allopurinol and probenecid are used. If allopurinol is not tolerated because of allergy, probenecid can be used. Recurrent attacks of gout can be prevented by controlling the body weight and limiting the consumption of alcohol and seafood/meat.

Ongoing treatment (Tophaceous gout)

The treatment mainly focuses on the re absorption of the uric acid from the surface of tophi, resulting in lowering of plasma urate concentration. Uric acid concentration is thus maintained within the middle of the optimal range by promoting its more excretion and reducing its production. This requires long-term use of urate-lowering drugs over many years. If joints are paining from an attack, physicians may prescribe NSAIDs, colchicine or oral corticosteroids, depending on the patient's acceptability. To prevent recurrent attacks, patient may be prescribed uricosuric agents. In rare cases, surgery is done to remove large tophi. The home based remedies and a perfect anti-gout diet have worked wonders in providing permanent relief from gout.

Medicines

Medicines for gout include:

- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Colchicine
- Corticosteroids
- Adrenocorticotropic hormone (ACTH)
- Allopurinol
- Probenecid
- Sulfinpyrazone
- Uloric (Febuxostat)
- Krystexxa (Pegloticase)[18]

NSAIDS, specifically indomethacin (Indocin), diclofenac and naproxen (Naprosyn*)* are commonly the first line medicines prescribed for treatment of gout. They can decrease inflammation as well as pain in joints and other tissues. Other NSAIDS may be equally effective. Initially maximum dosage is prescribed but as soon as symptoms subside dosage is reduced. COX-2 inhibitors such as celecoxib (Celebrex) can also be used for patients with gastrointestinal concerns but

their use for acute gout has not been specifically reported yet. On the basis of two studies of rigorous design and adequate size, etoricoxib is as efficacious as indomethacin for gout[19], with fewer adverse events. Etodolac 600 mg daily was found to be as effective as naproxen (500 mg twice or three times a day) in the treatment of acute gout. On the basis of a single small trial, meclofenamate sodium was found equally efficacious as indomethacin. They are usually not first option in persons with chronic renal disease as they can worsen renal function temporarily or permanently, cause fluid retention and increase blood pressure dramatically[12]. Colchicine (Colcrys) is used to treat acute flares of gouty arthritis and to prevent recurrent acute attacks. Colchicine is usually reserved for those patients, who are sensitive to NSAIDs Colchicine prevents or relieves gout attacks by reducing inflammation (Figure 3). It does not cure gout or lower the amount of uric acid in the body. It may be used in 2 ways, either take small amounts (1.8 mg total over 1 hour) regularly for months or years, or take large amounts (4.8 mg total over 6 hours) of colchicine during a short period of time. However, colchicine can cause nausea, vomiting, diarrhea and other side effects. Side effects may be less frequent with low doses.

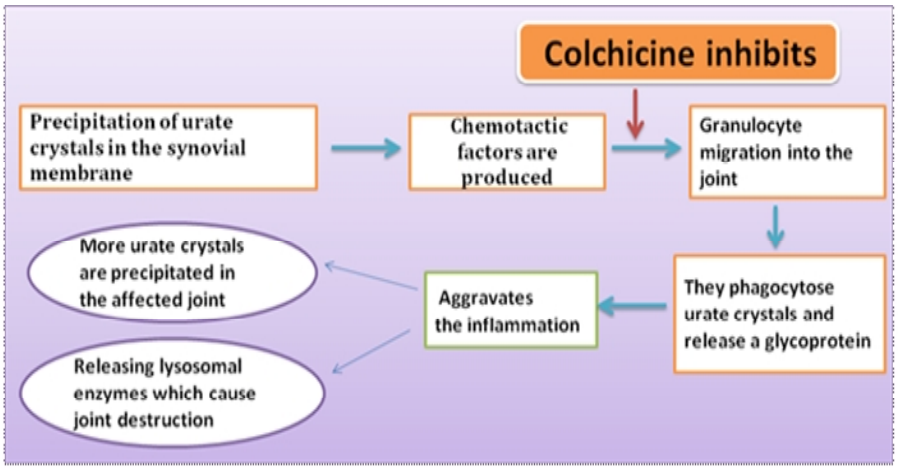

Figure 3: Mechanism of action of Colchicine

Patients with kidney or liver disease, or who are taking drugs that affect colchicine metabolism, must take lower doses of colchicine. Higher dose should be avoided as it is poisonous in nature. Corticosteroids or adrenocorticotropic hormone can be used for patients, who show resistance to NSAIDS or colchicine. They provide rapid relief from pain associated with gout, therefore they are not meant for long term usage. Intra-articular corticosteroids are particularly helpful in acute gout and improvement is seen within 24 h. But, if many joints are affected, systemic corticosteroids are a better option[6]. Patients with acute gout typically receive daily doses of prednisone (Meticorten, Sterapred, Sterapred DS) (20 – 40 mg) or its equivalent for 3 to 4 days, then it is tapered gradually over two weeks. ACTH is administered as an intramuscular injection. The side effects associated with corticosteroids are fluid retention in body, weight gain, osteoporosis, bruising, thinning of the skin and muscle weakness. Furthermore, corticosteroids should be avoided in patients suffering from the symptoms of diabetes, glaucoma, bone marrow disease, impaired liver and kidney function and cardiac diseases. Pregnant and breastfeeding women are also advised to stay away from these drugs. Allopurinol (Zyloprim, Lopurin) is prescribed for chronic gout. It is used to prevent gout attacks. Allopurinol blocks production of uric acid (Figure 4) and is the most common drug used to normalize blood levels. It is currently the gold standard of maintenance therapy.

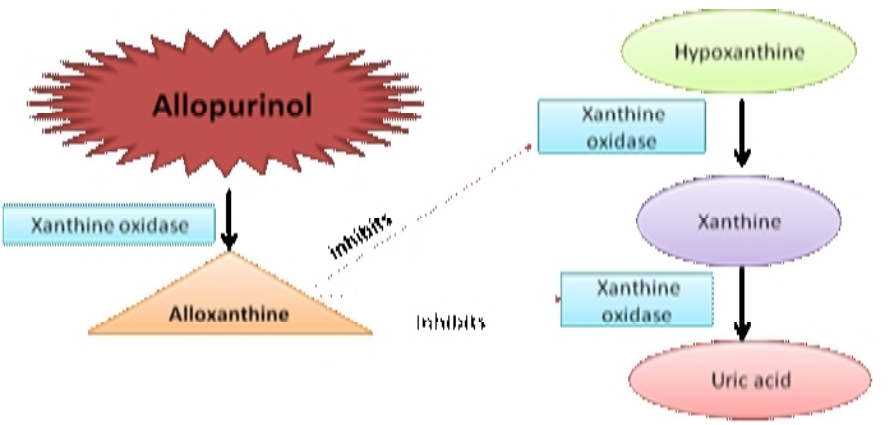

Figure 4: Mechanism of action of Allopurinol

Common side effects include stomach pain, headache, diarrhea and skin rash. Patients with chronic heart failure and gout, when treated for long term with low dose of allopurinol had higher mortality than patients without gout[6]. Probenecid (brand names - Benemid, Probalan) is prescribed for chronic gout. Probenecid is known as a uricosuric agent. Uricosuric drugs compete with urate for the brush-border transporter, thereby inhibiting its reabsorption *via* the urate-anion exchanger system. It competitively blocks active transport of organic acids by OATP at all sites. Thus, it promotes uric acid excretion and reduces its blood level. One should drink at least 2 liters of fluid per day while taking probenecid for preventing uric acid kidney stones formation. The starting dose is 250 mg twice daily, which is increased over 2 weeks to 500 to 1000 mg twice daily. Col Benemid (other brand names are Col-Probenecid and Proben-C) is a gout medication that contains Probenecid and Colchicine. Mild gastrointestinal irritation, Rashes and other hypersensitivity phenomena are rare. Only patients with good general kidney function should take probenecid. Sulfinpyrazone (Anturane) is another uricosuric agent prescribed to treat gouty arthritis. It actively inhibits the renal tubular re absorption of uric acid and reduces the renal tubular secretion of many other organic anions. Initial dosage of 100 to 200 mg is given twice daily. After the first week, the dosage may be gradually increased from 200 to 800 mg per day, divided in two to four doses to be taken with meals or milk. Gastrointestinal irritation, rashes and other hypersensitivity reactions are less common. Sulfinpyrazone is not currently available in the U.S. Benzbromarone is a potent uricosuric agent that is used in Europe. It is a reversible inhibitor of the urate-anion exchanger in the proximal tubule. It is absorbed readily after oral ingestion, and peak concentrations in blood are achieved in about 4 hours. It is metabolized to monobromine and dehalogenated derivatives, both of which have uricosuric activity, and is excreted primarily in the bile. As the micronized powder, it is effective in a single daily dose of 40 mg to 80 mg. It is effective in patients with renal insufficiency and may be useful clinically in patients, who are either allergic or refractory to other drugs used for the treatment of gout. Rasburicase (ELITEK) is a recombinant urate-oxidase, produced by a genetically modified *Saccharomyces cerevisiae* strain that catalyzes the enzymatic oxidation of uric acid into the soluble and inactive metabolite allantoin. It has been shown to lower urate levels more effectively than allopurinol. It is indicated for the initial management of elevated plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies. Its use, however, is limited, as it triggers an auto-immune response. The recommended dose of rasburicase is 0.15 mg/kg or 0.2 mg/kg as a single daily dose for 5 days, with chemotherapy initiated 4 to 24 hours after infusion of the first rasburicase dose. Febuxostat (Uloric), a new serum uric acid lowering drug, has shown good results[20]. It also acts by blocking production of uric acid and is a recent alternative[12]. Febuxostat is not significantly metabolized by the kidneys therefore; it might have advantages over allopurinol in patients with underlying kidney disease. Febuxostat should not be taken with 6-mercaptopurine (6-MP), or azathioprine. Pegloticase (Krystexxa) or PEGylated uricase is a new intravenous medication that is used to lower uric acid blood levels in certain patients with chronic gout. This infused medication (given every two weeks) is to be considered only for those patients, where in treatment with conventional uric-acid-lowering medications has failed since, it can cause anaphylactic reactions and infusion reactions. Lot of research is in progress to develop new and safe medicines to manage the symptoms of gout[9]. Losartan, (brand names - Cozaar and Hyzaar), is not specifically a gout medication but is an angiotensin II receptor antagonist, anti hypertensive drug that may help control uric acid levels. Fenofibrate, (brand name - Tricor), is not a specific gout medication, but it is a lipid-lowering drug that may help lower uric acid levels. Urate oxidase may lower uric acid levels by changing uric acid into an absorbable molecule. This medicine is currently being evaluated in the United States.Y-700 medicines decrease the amount of uric acid the body makes. These medicines are being studied and may be used in people who cannot take allopurinol. A number of new medications that are under study for treating gout include anakinra, canakinumab, and rilonacept.

Self help

One should have a positive outlook towards life. It is important for the gout patients to adopt a healthy life-style and undertake activities like meditation, proper diet, regular exercise program coupled with avoidance of soft and hard drinks, which aggravate the gout symptoms. Keep the joint cool by applying ice pack or bag of frozen vegetables wrapped in a towel (Do not apply directly to your skin without a towel as this could damage your skin). Do not cover the joint. This may provide help to ease the pain and swelling.

Surgery

In some individuals, gouty symptoms occur off and on for a long period of time. If these symptoms are not treated for more than 10 years, tophi are formed in the joints. These tophi can cause infection, pain, or deformation of joints. If medicines have been unsuccessful in shrinking or eliminating the tophi, surgery (excision) becomes a necessity to remove them.

Holistic Remedies

A conscious diet and regular exercise help in long term management of gout. Holistic remedies of gout help by reducing the synthesis of uric acid, thereby reducing inflammation swelling and pain. Holistic treatments also help in lowering uric acid levels in the body by flushing the system or neutralizing the uric acid.

Natural medications for uric acid gout

Gout has many causes, but it can be controlled and the symptoms can be curtailed significantly. The benefits of vitamins and herbs for the treatment of gout have plenty of anecdotal evidence. Vitamin - C: Intake of citrus fruits rich in Vitamin C remains as the best and cheapest form of treatment of gout. Vitamin C is believed to reduce the levels of uric acid in the body[11]. It stimulates the production of calcium carbonate, which in turn reduces acids in the body. It not only detoxifies the body by removing the uric acid from painful joints but also strengthens our immunity against various diseases. Dr. Hyon K. Choi, from the University of British Columbia, Vancouver, Canada, has found that high vitamin C levels are closely linked with a lower risk of gout, and dietary increases in this vitamin may prevent the development of gout[21]. Coffee: Drinking more than four cups of coffee in a day significantly lowered serum uric acid levels, to an extent of 8 % at maximum[22]. Fruits: Eating more of the dark-colored

fruits like raspberries, blueberries, purple grapes and blackberries have proven beneficial in the management of gout. Cherries are recommended for patients of gout because it is known to reduce inflammation in particular and possesses anti oxidant properties. Anthocyanin is the pigment in cherries that makes them red. They help the body to neutralize the already secreted uric acid and dissolve uric acid crystals so that kidneys can excrete them. Sweet cherries, such as Bing Cherries are very dark, they contain more anthocyanin and are believed to be the best cherries for gout. Cherries are also high in potassium that creates an alkaline state in the body, which helps to neutralize the already secreted uric acid. Drinking two to three glasses of cherry juice during an attack and one glass a day for maintenance, work well for many gout sufferers. They are safe to consume and have no side effects as do many prescription medications used to treat gout. Eicosapentaenoic acid (EPA): It is known to reduce chronic inflammation. Folic acid: Some studies indicate that folic acid may be helpful in inhibiting the enzyme needed to synthesize uric acid. Pycnogenol: It is found in the seeds of red grapes. It is an herb that was extracted from the bark of a French maritime pint tree. The active ingredients can be extracted from other sources including peanut skin, grape seed and witch hazel bark. It is a powerful anti oxidant that has a similar effect to vitamin C in the body. However, it is twenty times more effective than vitamin C in the body and fifty times stronger than vitamin E. The Memorial Sloane Kettering Center notes that pycnogenol may lower inflammation by lowering the production of inflammatory proteins. Due to its strong anti inflammatory characteristics, it is being used as treatment to reduce the symptoms and, in conjunction with diet and exercise, prevent a recurrence of a number of illnesses and conditions. Grape fruit juice: There are several benefits for grape fruit juice for gout. The fluids flush the uric acid from the joints, alleviating the pain and decreasing the chance of having another occurrence. Grape fruit juice for gout contains fruit flavors and nutrients. In addition, the grape fruit juice for gout increases the level of vitamin C, or ascorbic acid, which helps prevent gout attacks. Turmeric: Due to its anti-inflammatory and pain relieving properties, many cultures have used it as a remedy for gout. Results of a study published in the Journal of Alternative and Complementary Medicine shows that Curcumin, the active ingredient in turmeric, is as helpful as the anti-inflammatory drug ibuprofen to treat osteoarthritis. Curcumin is responsible for inhibiting the production of prostaglandins, which is related to pain. It is a potent anti-inflammatory and offers natural pain relief for gout. It is also a powerful anti oxidant and decreases the inflammatory enzyme called COX-2. Curcumin allows the body's adrenal gland to produce more of the body's own cortisone, a powerful reliever on inflammation and pain. Turmeric for gout is generally safe but can have side effects including nausea and diarrhea. Ginger: It act as a natural anti-inflammatory agent, which reduces the potential swelling of joints that may be affected by uric acid buildup. Calcium: The effects of calcium, when taken in moderate amounts can have an overall positive effect on the body. Calcium is combined with a healthy diet and exercise to keep the joints flexible. This method has proven effective in reducing the attacks of gout and even preventing gout from reccurring[11]. But consuming too much calcium can lead to a condition known as pseudo-gout. Therefore, one should consult a doctor before taking calcium. Xanthine Oxidase inhibitors: Apigenin, a flavonoid found in high amounts in parsley, thyme, and peppermint. Apigenin is a potent inhibitor of xanthine oxidase (catalyses the oxidation of hypoxanthine to xanthine and then to uric acid). Chrysin, luteolin, quercetin, kaempferol, myricetin, and isorhamnetin are other flavonoids that also inhibit xanthine oxidase activity[23]. The methanol extract of the twig of *Cinnamomum cassia* (*Chrysanthemum indicum*) and the leaves of *Lycopus europaeus* inhibits xanthine oxidase enzyme. Among the water extracts, the strongest inhibition of the enzyme was observed with that of the rhizome of *Polygonum cuspidatum*. Apart from above mentioned natural remedies, there are many other herbs used for treating Gout. One can use herbs as dried extracts (capsules, powders, teas), glycerites (glycerine extracts), or tinctures (alcohol extracts). Make teas with 1 tsp. herb per cup of hot water. Cover for a period of 5 - 10 minutes for leaf or flowers, and 10 - 20 minutes for roots. Drink 2 - 4 cups per day. One may like to take these tinctures alone or in combination. Herbs are also applied to the affected joint. Extract of stinging nettle can be applied to the joint to relieve pain. A poultice of birch leaves applied to the affected area for one to two hours a day will help relieve stiffness, pain and swelling. St. John's Wart oil can be massaged into joint and a poultice of crushed red cabbage applied overnight.

- Cranberry (*Vaccinium macrocarpon*) standardized extract, 300 - 400 mg daily, for kidney function.
- Green tea (*Camelia sinensis*) standardized extract, 250 - 500 mg daily, for antioxidant and immune effects.
- Devil's claw *(Harpagophytum procumbens),* standardized extract, 750 mg 3 times daily, for pain and inflammation.
- Cat's claw (*Uncaria tomentosa*) standardized extract, 20 mg 3 times a day, for inflammation, immune, and antibacterial / antifungal activity.
- Bromelain (*Ananus comosus*) standardized extract, 40 mg 3 times daily, for pain and inflammation. Celery seed or celery seed extract can stimulate the removal of uric acid.
- Gravel root (*Eupatoriumpu1pureum*) is used for the removal of uric acid.
- Juniper berry is a diuretic which increases urine production, thus eliminating excess uric acid.
- Nettle root helps the kidneys eliminate uric acid.
- Pine Bark extract act as in anti-inflammatory decreasing pain and stiffness.

Nutritional supplements

Vitamins such as A, C, E, B-complex vitamins, and trace minerals such as magnesium, calcium, zinc and selenium are good for preventing gout. Magnesium and B- complex vitamins are important for proper liver function. The liver produces enzymes and acids that aid in the digestion of proteins.

- Omega-3 fatty acids, such as fish oil, 1- 2 capsules or 1 tablespoons of oil daily, help to decrease inflammation and promote general health.
- Cod liver oil is high in vitamin A and helps to keep the kidneys healthy and prevents the built up of uric acid inside the body. Consuming one teaspoon daily can help to prevent gouty arthritis.
- Rosemary oil massaged into the skin of the affected joint can give immediate relief from pain. It can be diluted with olive oil if it irritates the skin.
- Watermelon and its seeds are used in the treatment of gout[1].
- Cultured cabbage juice, active yogurt or a beneficial bacteria supplement such as PB-8 or Jarrodophilus will

maintain healthy intestinal flora. These bacteria consume uric acid before it is absorbed by the intestines and enters the blood stream.

- Baking soda is used to raise the alkalinity of body fluids allowing more uric acid to be dissolved in the urine so that it can be expelled out of the body. Dissolve half a teaspoon in 8 ounces of water and drink four to six times a day during an attack
- Methylsulfonylmethane (MSM), 3,000 mg twice a day, helps to decrease inflammation.
- Milk does not worsen the gout, rather it can help. Milk contains orotic acid, which promotes renal urate excretion and could contribute to urate-lowering effects of dairy products. Some of the possible mediators of urate-lowering effect of dairy products are calcium, phosphorus, magnesium, lactalbumin, casein, lactose and orotic acid[11].

Physical Medicine

- Hot and cold compresses - Alternating hot compress for 3 minutes with a cold one for 30 seconds provides pain relief and increases circulation. Heat packs have been tried in relieving the pain and swelling of gout.
- For a hot and swollen joint, support it with a cane or something similar to provide some relief and put off your weight from that paining joint.
- The mixture of a cup of vinegar with one teaspoon of pepper and some water is also considered as one of the effective home remedies.
- Another form of many home remedies is to have a foot bath with warm water mixed with extracts of ginger or Epsom salt. One can keep his/her foot immersed in the same for 30 minutes.
- Massaging your foot gently by pressing the area between the bottom of the big toe and the ball of the foot is another effective home remedy.
- Application of bandage made of charcoal powder and grounded flax seeds, or wheat and mustard powder may prove beneficial in gout.

Acupuncture

Acupuncture may help in managing pain associated with gout.

Lifestyle changes

Relaxation techniques like medication, yoga, deep breathing exercises and other similar activities should be adopted by the patient in his routine. These activities will help to cope up with gout.

Occupational therapy

The occupational therapist provides services to people with gouty arthritis and makes them capable to cope up with activities of daily living. The primary aim of occupational therapy is to develop the skills and capacity of the patient so that he/she is able to master the tasks essential at home or work. The therapist can provide advice on how to make life simpler and conserve energy while protecting the joints.

Orthotist

One must wear appropriate, comfortable and supportive footwear that can eliminate pain while walking.

Reflexology for Gout

A reflexology practitioner massages the appropriate area at the centre of the sole of foot. This helps in restoring function of the kidneys and spleen, which are responsible for uric acid production.

Hydrotherapy or pool therapy

Buoyancy of water is made use of to provide comfort to the patient and assist in movements of the affected joint.

Psychology

The development of gout can cause depression. Therefore, a psychologist builds up a positive attitude in patients.

Homeopathic remedies

Homeopathic medications are used in minute doses that are non-toxic. Therefore, they are considered safe for gout. They are numerous and easily available (Table 2). They are usually inexpensive and easy to use and are based on the symptoms of gout that you are treating. Before prescribing a remedy, homeopaths take into account constitutional type - physical, emotional, and psychological make-up of the patient. There are many homeopathic medications for gout such as Arnica, *Aconitum napellus*, Belladonna, *Benzinum acidum*, *Berberis vulgaris*, Bryonia, Guaiacum, *Pulsatilla nigricans*, Rhododendron, Sabina and Sulphur. Several herbs are also considered valuable in the homeopathic treatment of gout including hawthorn, devils claw, parsley, hyssop, juniper, Hydrangea, ginger, saffron, alfalfa, red clover, spearmint and yarrow. The use of apple cider vinegar, baking soda and fish oil are also said to provide relief. One homeopathic remedy for gout is the triple knock out (TKO), which provides three powerful pain management supplements.

Table 2: Various Homeopathic Remedies for Gout

Homeopathic remedy	Application
Nux vomica	Gout that causes irritability and impatience
Ledum	Gout located in the big toe
Colchicum autumnale	Red, inflamed, painful joint
Aconite	Gout of the legs and feet and gout that flares up during cold weather
Rhus toxicodendron	Sudden excessive swelling, stiffness of the joint and throbbing pain
Calcera fluorica	Swollen joints of fingers and toes
Arthritin	Inflammation, swelling and stiffness of joints

Notable Victims

- Alexander the Great (The world conqueror)
- Christopher Columbus (A great explorer)
- Leonardo Da Vinci (The great artist- made Mona Lisa)
- King Henry VIII of England (The British king, lived from 1491 to 1547, was overweight)
- Benjamin Franklin (The 18th century Renaissance man, discovered electricity, invented bifocals, was one of the founding fathers of the United States and had gout)
- Sir Isaac Newton (English mathematician and physicist, experienced gout attacks in both his feet, just two years before his death)
- Samuel Johnson (British author and poet suffered from gout, when he was 65)
- Harry Kewell (An Australian professional soccer player, was 27 when he was diagnosed with gout while playing in the 2006 World Cup)

- David Wells (A left-handed pitcher has played for the New York Yankees and Toronto Blue Jays and has struggled with gout throughout his baseball career)

Key Points

- Gout is manifested by terrible, unexpected, severe pain and swelling.
- Management of gout includes strategies to reduce the joint pain and intake of medicines, which lower the level of uric acid in body fluids.
- Avoid alcohol consumption and foods rich in purines.
- Drink plenty (six to eight glasses) of water a day.
- Use healthy cooking oils, such as olive oil or vegetable oil.
- Maintain a regular exercise schedule and control body weight.
- Keep blood pressure under control, as it can trigger gout flare ups.
- One must be careful so as to not damage the affected joint.

Avoid rapid/sudden fasting as this can raise uric acid levels.

Table 3: General Guidelines for Gout Prevention

1.	Eat high fiber diet.
2.	Purine-rich foods should be avoided (e.g. red meats, sweet breads, vegetables like asparagus, broccoli or artichokes). Potential food allergens (including dairy products, wheat, corn, preservatives, and food additives) and refined foods (such as white breads, pastas) should be eliminated from diet.
3.	Cut down on trans-fatty acids, found in commercially baked goods and nutrients containing oxalates, such as spinach, rhubarb, beets, nuts, chocolate, black tea, wheat bran, strawberries, and beans.
4.	Avoid sugar/soft drinks.
5.	Eat anti-oxidants like fruits and vegetables that are rich in Vitamin C.
6.	Take foods having high content of magnesium, low in calcium content, such as barley, bran, corn, rye, oats, soy, brown rice, avocado, banana, and potato.
7.	Eat foods that are rich in potassium (spinach, avocado, dried peaches, bananas, orange juice, carrots, a baked potato, kidney beans, lima beans, yams, cantaloupe or dried yams).
8.	Exercise at least 30 minutes daily for 5 days a week.
9.	Avoid alcohol and tobacco.
10.	Drink plenty of water (2-3 liters per day) to help flush uric acid through the kidneys.

Table 4: Gout v/s Pseudo gout

Gout	Pseudo gout
• Gout is due to inflammation caused by monosodium urate monohydrate (MSU) crystals • Usually the big toe gets swollen first. Elbow, wrist and small finger joints are common sites for gout. • Urate crystals get deposited in joints and tissues, when there is excessive production or under excretion of uric acid. • Gout is aggravated by certain medicines such as thiazides, diet rich in purines and alcohol intake. • Kelley-Seegmiller syndrome or Lesch-Nyhan syndrome or von Gierke disease is commonly associated with gout. • Joint instability is common.	• In Pseudogout, inflammation is caused by calcium pyrophosphate (CPP) crystals and is sometimes referred to as calcium pyrophosphate disease (CPPD) • It is more common in wrist/knee joint. • Pseudogout is caused by calcium pyrophosphate dihydrate (CPPD) salt accumulation. • No such specific cause is identified for pseudogout. • Pseudogout is associated with thyroid or parathyroid dysfunction and with iron overload (hemochromatosis). • Joint instability is not observed.

CONCLUSION

Gout is well known in medical circles as “the King of diseases and the Disease of the kings” because of its occurrence among the rich and powerful and its link with wine and meat. The intense pain experienced during an acute attack of Gout is just unbearable. The inflammation of the tissues around the joint causes the skin to become swollen, tender and sensitive to even a slight touch. Even a thin cloth/saree draped over the affected area causes extreme pain. Intense pain, redness and swelling around the joint area are the main symptoms of gout. Tendency to develop gout and elevated blood uric acid levels (hyper uricaemia) is often inherited. It is aggravated by obesity, alcohol intake, high blood pressure, soft drinks, abnormal kidney function and by certain medications such as thiazides, aspirin etc. Trauma, injury, dehydration and fever precipitate the attacks of gout. The most reliable diagnostic test for gout is the identification of urate crystals in joints, body fluids, and tissues. An attack of gout is managed with, drug therapy (allopathic as well as holistic) non-drug therapy, self help and surgery. Holistic approach often works wonders in relieving the symptoms of gout.

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