EPIDEMIOLOGY CLINICAL FEATURES AND COMORBIDITIES IN GOUT

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CERTIFICATE

This is to certify that the dissertation titled **"EPIDEMIOLOGY CLINICAL FEATURES AND COMORBIDITIES IN GOUT"** is the original work done by **Dr. KIRTHI.R**, post graduate in D.M., (Rheumatology) at the Department of Rheumatology, Madras Medical College, Chennai-3 to be submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai-32, towards the partial fulfillment of the requirement for the award of D.M.., Degree in Rheumatology, August 2008.

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INTRODUCTION

HISTORICAL BACKGROUND

Gout is an inflammatory arthritis mediated by crystallization of uric acid within the joints. Gout has been called the king of kings and the disease of kings. The term gout introduced in the thirteenth century is derived from the Latin word “Gutta”a drop and reflects the early belief that a poison falling drop by drop into the joint was responsible for the disease. Hippocrates described gout as podagra, chiegra, gonagra depending on the site of involvement, the foot the wrist or the knee. Tophi were first described by Galen. Thomas Sydenham’s unsurpassed description marked the modern clinical history of gout. Wollartanin (1797) and Pearson (1798) demonstrated urate in the tophi of patients with gout. Leeuwenhock the inventor of the microscope first described these crystals in 1679. In 1848 Garrod demonstrated an increased amount of uric acid in the blood of gouty patients.

Today gout is used to represent a heterogenous group of diseases found exclusively in human species that includes:-

- Elevated serum urate concentration (hyperuricemia)
- Recurrent attacks of acute arthritis in which monosodium urate monohydrate crystals are demonstrable in the synovial fluid leukocytes.
- Aggregates of monosodium urate monohydrate crystals (tophi) deposited chiefly in and around joints which sometimes leads to deformity and crippling.
- Renal disease involving glomerular, tubular and interstitial tissues and blood vessels, uric acid nephrolithiasis

Hyperuricemia is a term representing an elevated level of urate in blood..This occurs in an absolute sense when the serum urate concentration exceeds the limit of solubility of monosodium urate in the serum, which is about 7mg/dl at 37.c.The serum urate concentration is

elevated in a relative sense when it exceeds the upper limit of an arbitrary normal range which is usually defined as mean serum urate value plus two standard deviations in sex and age matched healthy populations. In most epidemiologic studies the upper limit has been rounded off at 7mg/dl in men and 6mg/dl in women.

EPIDEMIOLOGY

The prevalence of gout is increasing globally. Hyperuricemia is fairly common with a prevalence ranging from 2.3 to 41.4 percent in various populations. .Serum urate concentrations vary with age and sex .Children has a concentration in the range of 3-4mg/dl because of high renal uric acid clearance. At puberty, serum urate concentrations increase by 1 to 2 mg/dl in males, with these higher levels generally sustained throughout life. The Incidence of gout increases with the age in both sexes. Serum urate levels also tend increase with aging in women, but the trend is less clear in men. Age associated risk factors for hyperuricemia and gout might explain to a certain extent the cause for increasing incidence of gout with older age. Although the prevalence and incidence of gout are substantially higher in men than women before menopause, the disease burden in women tends to approach that of men after menopause. The mechanism of lower serum urate levels in women is a consequence of sex hormones and is related to a higher fractional excretion of urate secondary to a lower tubular urate post secretory reabsorption.

A variety of factors appear to be associated with higher serum uric acid concentrations. In adults, serum urate levels correlate strongly with the serum creatinine and urea nitrogen levels, bodyweight, height, age, blood pressure and alcohol intake. Body weight has proved to be one of the most important predictors of hyperuricemia in people of widely differing races and cultures with rare exceptions.

The incidence of gout varies in populations, with an overall prevalence of less than 1 to

15.3 percent and appears to be increasing. The prevalence seems to be increasing substantially with age and increasing serum urate concentration. The annual incidence of gout is 4.9 percent for urate levels greater than 9mg/dl, 0.5 percent for values between 7 and 8.9mg/dl, and 0.1percent for values less than 7mg/dl.For serum urate values greater than 9mg/dl, the cumulative incidence of gout reaches 22 percent after 5 years.

CLINICAL FEATURES

In the complete development of its natural history gout passes through four stages, asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. The usual presentation is acute attacks of exquisitely painful arthritis usually monoarticular during the initial attacks associated with a few constitutional symptoms .Subsequently the attacks become polyarticular and lasting for a variable but limited time and separated completely by asymptomatic intervals. Attacks recur at progressively shorter intervals and eventually resolve incompletely leaving in a train of chronic arthritis which slowly progresses to a crippling disease on which acute exacerbations are superimposed.

ACUTE GOUTY ARTHRITIS

The peak age of onset of acute gouty arthritis was in the fourth, fifth or sixth decade in various studies. Onset before the age of thirty should raise the question of an unusual form of gout perhaps related to a specific enzymatic defect causing over production of purines or rarely to a unususal form of parenchymal renal disease. In 85 to 90 percent of first attacks a single joint is involved. In atleast, half of the initial acute attacks, the first metatarsophalangeal joint is the site of the involvement.

Both the great toes were involved simultaneously in 5 percent of subjects in the first

attack. Percentage of initial attacks of polyarticular gout was variable. Ninety percent of patients with gout experience acute attacks in the great toe at some during the course of their disease. Next in frequency are the insteps, ankles, heels, knees, wrists, fingers, and elbows. Gout is predominantly a disease of the lower extremity but any joint may be involved. Rare sites are shoulders, hips, spine, sacroiliac, sternoclavicular and temporomandibular joints. The more distal the site the more typical is the character of the attack. Acute gouty bursitis also occurs and mainly involves the prepatellar and olecranon bursa. Urate deposition and subsequent gout appear to have a predilection for previously damaged joints. Gout occurs in the heberdens nodes of older women.

In most patients, the initial attack occurs with an explosive suddenness and commonly begins at night after the individual has gone to a good sleep. Within a few hours after onset, the affected joint becomes hot, dusky red, swollen and extremely tender. Occasionally, lymphangitis may develop. Systemic signs of inflammation may include leukocytosis, fever, and elevation of ESR. The course of untreated acute gout is variable.

Mild attacks may subside in a few hours or persist for a day or two and never reach the intensity described for classic attack. Severe attacks may last for days to weeks. The skin over the affected joint may desquamate as the attack subsides. With resolution, the patient becomes asymptomatic and enters the intercritical period.

The definitive diagnosis is established by aspiration of the joint and identification of intracellular needle-shaped crystals that have negative birefringence with compensated polarized light microscopy, but criteria have been proposed for the presumptive diagnosis, which are triad of acute monoarticular arthritis, hyperuricemia, and a dramatic response to colchicines therapy; along with the criteria proposed by American college of Rheumatology.

Intercritical gout

This is the period between gouty attacks. Some never have a second attack. The frequency of gout attacks usually increases with time in untreated patients. Later attacks have a less explosive onset, more severe, last longer abate more gradually & usually polyarticular. Nevertheless, recovery is complete.

Radiographic changes develop during the intercritical period despite no sign of tophi on physical examination. These changes are more likely in those with more severe hyperuricemia and more frequent acute attacks. The diagnosis of gout in a hyperuricemic patient with a history of acute attacks of monoarthritis may be difficult or inconclusive during the intercritical phase.

Aspiration of an asymptomatic joint, however can be a useful adjunct in the diagnosis of gout if urate crystals are demonstable. Joint fluids obtained from gouty patients during intercritical phase revealed monosodium crystals in 12.5 to 90 percent of the joints. Such crystals in asymptomatic joints are often associated with mild synovial fluid leukocytosis, which suggests the potential for contribution to joint damage even in the interval between attacks.

CHRONIC TOPHACEOUS GOUT

When recurrent acute gout and hyperuricemia go untreated and when there is a failure to eradicate causative factors such as alcohol excess, obesity or diuretic therapy, the condition may evolve from a picture of sporadic acute mono and oligoarthritis through recurrent polyarthritis to persistent low grade joint inflammation, joint deformity and deposition of urate crystals to form visible tophi. The time from the initial attack to the beginning of chronic symptoms or visible tophaceous involvement is highly variable in studies of untreated patients. The intervals range from 3 to 42 years with an average of 11.6 years between first attack and

the development of chronic arthritis .Ten years after the first attack, about half of the individuals were still free of obvious tophi, and most of the remainder had only minimal deposits. Thereafter the proportion of those with non tophaceous involvement slowly declined to 28 percent after 20 years.

Two percent of the patients had severe crippling disease some 20 years after the initial attack. The rate of formation of tophaceous deposits correlates with both the degree and the duration of hyperuricemia. The principal determinant is the serum urate levels. The rate of tophus formation also increases with the severity of renal disease and the use of diuretics.

Tophaceous gout is the consequence of the chronic inability to eliminate urate as rapidly as it is produced .As the urate pool expands, deposits of urate crystals appear in cartilage, synovial membranes, tendons, soft tissue and else where. Tophi are rarely present at the time of initial attack of primary gout, but have been observed in gout secondary to myeloproliferative diseases, in juvenile gout complicating glycogen storage diseases, in Lesch-Nyhan syndrome, or after renal allograft transplantation in patients treated with cyclosporine.

Tophaceous deposits develop within the same joints affected by acute gout and especially the first metatarsophalangeal joint .The relatively mild discomfort of chronic gout may be punctuated by episodes of acute arthritis. About one third of chronic gout patients develop visible tophi. The process of tophaceous deposits advances insidiously. No synovial joint is immune to this process. Although the joints of the feet are notoriously involved in the acute illness, it is the hands where evidence of chronic gout is more evident. Eventually, extensive destruction of the joints and large subcutaneous tophi may lead to grotesque deformities, particularly of the hands and feet and progressive crippling.

Swelling of the distal and proximal interphalangeal and metacarpophalangeal joints are

often due to articular and periarticular tophi. Swan neck, Buttonierre and flexion deformities may develop resembling rheumatoid arthritis. The diagnosis is suggested by the pallor of tophaceous material beneath the skin which is stretched over an involved joint. Toes, ankles, elbows and wrists may be similarly affected. Within the joints, tophi contribute to the development of bone erosions especially in the big toe but also elsewhere. Tophi are classically found on the pinnae, the elbows, the Achilles tendon as fusiform enlargements but they may be distributed more widely, occurring within and around the finger joints, in the finger tip pulp, around the knee and within olecranon and prepatellar bursae .Spinal joints do not escape urate deposition but acute gouty spondylitis is unusual. Symptoms related to nerve or spinalcord compression by tophi have been observed. Tophi may also occur in myocardium, valves, the cardiac conduction system, various parts of the eye and the larynx. Careful inspection of tophi may reveal a white subcutaneous granular appearance due to accumulation of monososium crystals. Tophi emerge at unexpected sites becoming suddenly visible and discharging uric acid crystals as a paste or pus like material especially during hypouricemic treatment

hyperuricemia and associated disease

The association of hyperuricemia and gout with other important disorder continues to be documented. Studies in rats, has led to reconsideration of a pathogenic role for hyperuricemia independent of crystal deposition in hypertension, chronic kidney disease cardiovascular disease (coronary heart disease, stroke and peripheral artery disease, and congestive heart failure), and aberrant metabolic states, such as hypertriglyceridemia, obesity, insulin resistance, and metabolic syndrome. Whether or not hyperuricemia (or even “high normal” serum urate levels) plays a causal role or simply is a marker arising in the course of each related disorder remains unresolved.

Hyperuricemia and hypertension

An association of hyperuricemia and hypertension long has been recognized and is supported by the following observations.

- Prevalence of hyperuricemia of approximately 20% to 40% in untreated hypertensive patients and approximately 50% to 70% in treated or renally impaired hypertensive patients
- Gout prevalence's of 2% to 12% in hypertensive patients
- 25% to 50% hypertension prevalence's in groups of patients who have documented gout
- Increasing prevalence of hyperuricemia with increasing blood pressure in the general population.
- Increasing risk of development of hypertension with increasing baseline serum urate levels.

Therefore, the association between hypertension and hyperuricemia may be related to the reduction of renal blood flow in hypertension. In addition, uric acid causes smooth muscle proliferation in vitro and vascular disease in animal.

Renal disease

Twenty to forty percent of patients with gout have albuminuria, which is usually mild and often intermittent. Hyperuricemia alone may be implicated as the cause of renal damage only when the concentration of urate chronically exceeds 13mg/dl in men or 10mg/ dl in women. Prior to the routine treatment of asymptomatic hypertension, renal failure accounted for 10 percent of the deaths in patients with gout. Today, it appears that moderate hyperuricemia has no direct harmful effect on renal function. Nevertheless, after gouty arthritis, renal problems appear to be the most frequent complication of hyperuricemia. These include urate nephropathy uric acid nephropathy, and nephrolithiasis.

The term urate nephropathy is used to represent the deposition of urate crystals in the interstitium of the medulla and pyramids with a surrounding giant cell reaction, a distinctive histologic finding characteristic of the gouty kidney. Factors such as coexistent hypertension, chronic lead exposure, ischemic heart disease, and primary preexistent renal insufficiency, probably play important roles in the pathogenesis of the pathology. Although urate nephropathy appears to exist as a distinct entity, it is not believed to be an important contributor to declining renal function in most gouty patient.

Uric acid nephropathy is the term used to represent acute renal failure resulting from the precipitation of large quantities of uric acid crystals in the collecting ducts and ureters. This complication most commonly occurs in patients with leukemia and lymphomas as a result of rapid malignant cell turnover, often during chemotherapy.

Nephrolithiasis occurs in 10 to 25 percent of patients with primary gout, prevalence greater than that in the general population. The likelihood of stones in a given patient with gout increases with the serum urate concentration and with amounts of urinary uric acid excretion. It exceeds 50 percent with a serum urate value above 13 mg/dl or with urinary uric acid excretion rates in excess of 1100 mg every 24 hours Uric acid stones do occur in patient with no history of gouty arthritis, and only 20 percent of this group are hyperuricemia. Other renal stone disease is associated with hyperuricemia and gout. Gouty subjects also have an increased incidence of stones that contain calcium.

In addition, about 30 percent of patients with recurrent calcium stone disease have either an increased urinary uric acid excretion rate or hyperuricemia. An etiologic link between uric acid and recurrent calcium oxalate stones is provided by the report of reduced stone frequency in such patients treated with allopurinol.

Hyperuricemia has been associated with other familial nephropathies, such as medullary cystic disease, focal tubulo interstitial disease, and polycystic kidney disease. In fact, gout develops in 24 to 36 percent of individuals with polycystic kidney disease. The hyperuricemia and gouty arthritis appear to precede the development of renal failure

hyperuricemia and cardiovascular disease

The association of hyperuricemia with the manifestations of atherosclerosis has led to speculation that hyperuricemia is a risk factor for coronary artery disease. Hyperuricemia is associated with increased cerebrovascular disease, cardiovascular disease, and cardiovascular mortality. Hyperuricemia is an independent risk factor for coronary artery disease. It seems likely that in patient with hyperuricemia, clinical correlates such as hypertension, insulin resistance, diabetes mellitus, hyperlipidemia, and obesity contribute meaningfully to the observed association between elevated serum urate concentrations and atherosclerosis. Whether urate levels simply help to identify these patients or play a primary role in the pathogenesis is unclear.

Hyperuricemia and metabolic syndrome

The term syndrome X has been applied to a cluster of abnormalities, including resistance to insulin-stimulated glucose uptake, hyper insulinemia, hypertension, and dyslipoproteinemia, that are characterized by high levels of plasma triglycerides and high-density lipoprotein cholesterol. Hyperuricemia closely correlates with the degree of insulin resistance and, therefore, is a likely feature of syndrome X. Syndrome X has been associated with coronary artery disease, and explains the previously recognized association between coronary artery disease and hyperuricemia.

BMI and waist-to-hip ratio were strongly associated with the risk for incident gout after adjusting for various confounders including dietary factor.

Adiposity

Adiposity has been noted to be associated with serum uric acid levels and proposed to increase the risk for gout. Factors not related to uric acid, such as chronic joint trauma resulting form excess weight, are proposed as an additional explanation for the association between obesity and gout.

hyperuricemia &hypothyroidism

There appears to be a significant increase prevalence of hypothyroidism among both female patient (25 percent) and male patients with gouty arthritis, in contrast to the rates in control subject (10 percent and 2 percent, respectively). Hyperuricemia may also be more prevalent in patients with hypothyroidism; Thyroid replacement therapy is associated with a decrease in serum urate concentration cause by an increased uric acid diuresis, a change not explained solely by a change in Creatinine clearance. Although the cause of hyperuricemia and gout inpatients with hypothyroidism is unknown, it is speculated that urate metabolism is mediated by thyroid stimulating hormone receptors in extra thyroidal tissues, including the kidney, and that these modulate urate homeostasis.

Other Connective tissue diseases

Gout is rarely seen in patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, or ankylosing spondylitis (AS). The basis for the decreased concurrence of these disorders is unclear, although the long-term use of non steroidal anti inflammatory drugs (NSAIDs) may mask the clinical features of gout in some of these patients.

Alcohol

Alcohol consumption has long been associated with hyperuricemia and gout. In susceptible persons, alcohol use can lead to the precipitation of acute gouty arthritis with a prevalence of hyperuricemia of 8.42 percent. Both a decrease in the renal excretion of uric acid and an increase in uric acid production seem to be important factors in this association. Ethanol increases uric acid production by accelerating the turnover of adenosine triphosphate (ATP). Among alcoholic beverages, beer may have more potent effects on uric acid production because of its high guanosine content.

Pathogenesis

Uric acid is a weak acid (pKa 5.8) that is present mainly as urate, the ionized form, at physiologic pH. As urate concentrations increase in physiologic fluids, urate can crystallize as a monosodium salt in oversaturated tissues, mainly within and around joints, but also in the skin or other structures, such as spinal ligaments and fibrous tissue. The physiochemical properties of monosodium urate (MSU) cause crystals to precipitate in body fluids if the concentration is greater than 6.8 mg/dl. The solubility of urate is modulated by temperature (lower temperature at the foot), intra-articular fluid dehydration (onset at night), and cat ion concentration. MSU crystallization is dependent on nucleating agents, such as insoluble collagens, chondroitin sulfate, proteoglycans, cartilage fragment, and other crystals. Tophus can grow from urate crystals depending on urate super saturation and on increased promoters or loss of inhibitors of crystallization.

MSU crystals are capable of directly triggering, amplifying, and sustaining and intense inflammatory response, a so-called “acute attack, “because of their ability to activate humoral and cellular inflammatory components. MSU crystals first are released in the joint cavity,

activating synovial lining cells, followed by the recruitment and activation of mastocyes and peripheral blood monocytes through endothelial cell activation. Auto limitation of acute inflammation is driven by macrophages, neutrophil necrosis, and apoptosis, followed in some cases by low - grade residual synovitis or by restitution ad integrum.

Initiation

Free crystals or even naked crystals with no protein coating are released form a remodeling tophus. Once released within the joint cavity, under specific local and systemic circumstances temperature, pH variations, local articular trauma, infection, or surgery, MSU crystals should interact with the synovial lining cells.

The fibroblast-like synoviocytes and macrophage-derived cells, has phagocytic properties. They can be opsonized by proteins and phagocytosed as particles, triggering a typical phagocytic inflammatory response .Initial mechanism involves the physicochemical surface properties of MSU particles interacting directly within minutes with membrane proteins and lipids, either physically or through electrostatic bounds because MSU crystals are negatively charged.

Membrane modulation leads to cross-linking and clustering of membrane as an initial event for activation of redundant signaling pathways, including G proteins, phospholipase C and D, tyrosine kinases associated with the FAK complex, and the three mitogen-activated protein kinases.

Crystal-induced cellular activation and recruitment

Neutrophils are the hallmark of inflammatory cells recruited into the synovial fluid in gouty attack; other cells also play a role. Monocytes recruited from the blood and resident

mastocytes are the first cells to infiltrate or be activated. Mast cells are proposed as plying a role in innate immunity and can be an important cell component of MSU CIA because they contain preformed granules with cytokines and also histamine, and acute phase reagent. Histamine is well documented as having multiple effects leading to increased vascular permeability and enhanced adhesion molecule expression, such as up regulating P-selectin, which medicates neutrophil adhesion and recruitments. Preformed and stored mastocyte mediators (e.g. platelet activating factor [PAF], vascular endothelial growth factor, TNF and IL-1 can activate endothelial cells, cell recruitment, and increase vascular permeability. Monocytes also are implicated in the early onset of MSU CIA. They infiltrate the tissues of animal models of MSU CIA at a rate 10 times higher than neutrophils.

MSU crystals actually have the ability to trigger and inflammatory response by freshly isolated monocytes and THP-1 monocytic cells, including TNF, IL-1, IL-6 and 8 (but not IL-10) secretion, which in turn promote endothelial cell E-selectin expression and secondary neutrophil adhesion under dynamic conditions. Angiogenic factors also have cytokine properties and are expressed in gout. High levels of angiogenin, an angiogenic factor with anti inflammatory properties, are measured in SF from patients who have gout. Monocytes play a central role in the regulation of acute attack, because they also are implicated in the self-limitation of inflammation.

Amplification

Neutrophils are recruited into synovium and migrate within the synovial cavity along with serum proteins. Activated endothelium allows neutrophil adhesion dependent on E-Selection and P-Selectin upregulation and migration into the synovium determined by effects of cytokines (TNF and IL-1∃) and chemokines (IL-8 and macrophage inflammatory protein-1∃). Neutrophils follow concentration gradients of chemoattractants, such as C5a and

IL-8.Spontaneous resolution of acute attack

Crystal properties can be modified and represent a first target: crystal size reduction and crystal clearance Macrophages (eg, resident and differentiated monocytes) should represent the major cell in this regulatory process. Mononuclear phagocyte may play a key role within the synovial compartment, tipping the balance from the asymptomatic state to acute inflammation, or vice versa, depending on the state of monocyte to macrophage differentiation.

A switch from homologous monocytes to macrophages leads to the loss of ability to produce pro inflammatory cytokines (IL-1, I1-6,and TNF-α) and conversely, to stimulate anti-inflammatory cytokine secretion (IL-10 and transforming growth factor [TGF] ∃1)when stimulated by phagocytosed MSU crystals. Under MSU crystal stimulation, macrophages produce IL-10 and, mainly, TGF-∃1, a pivotal cytokine in the anti-inflammatory process TGF-∃1 can lower endothelial activation, reduce monocyte and neutophil adhesion and recruitment and reduce IL-1 expression and IL-1 receptor expression.

TGF-∃1 secretion also can be triggered by ingestion of apoptotic cells. This monocyte-macrophage switch and its ability to control inflammation a well-known mechanism not related specifically to MSU crystals. The mechanisms underlying the anti-inflammatory switch are understood but it seems, for example, that the production of pro and anti inflammatory cytokines by phagocytic monocytes is regulated delicately during the ingestion of apoptotic cells as part of an intrinsic mechanism to prevent inflammatory auto immune reaction. Binding or phagocytosis of apoptotic cells, but not necrotic or lysed cells induce active anti-inflammatory or suppressive properties in human macrophages.

It is likely that resolution of inflammation depends not only on the removal of apoptotic cells but also on active suppression of inflammatory mediator production. Other anti-

inflammatory compounds also are released by MSU crystal stimulated macrophages, namely nitric oxide (NO) and peroxisome proliferators activated receptor (PPAR).NO inhibition maintains the inflammatory cellular reaction evidenced in vivo.

Therefore in MSU-crystal inflammation NO seems to act as an anti inflammatory compound. PPAR-c stimulation and production by adherent monocytes by MSU crystals can delay neutrophil apoptosis.

Intercritical gout

Although MSU crystals are the hallmark of gouty arthritis, they can be found even during the resolution phase but have lost their ability to stimulate further inflammation, and also between attacks, because they remain in the joint.

Chronic tophaceous gout

After years of chronic and untreated hyperuricemia, gouty arthritis can develop with its hallmark, intra articular and periarticular tophi. Gout tophi are characterized by foreign body granulomas consisting of mono and multinucleated macrophages surrounding deposits of MSU microcystals. After primary formation, granulomas grow with degradation of the extra cellular matrix. Once developed in situ in cartilage or in synovium, it is assumed that MSU crystals may contribute to chronic synovitis and associated joint damage. Tophi can grow at the cartilage surface and within the synovium, leading to low grade synovitis, even subsiding after clinical resolution of gout attacks or to foreign body synovitis around crystals, as evidenced by histologic studies. Direct cartilage-tophi contact is demonstrated by arthroscopy. Experimental studies related to topic pathogenesis are lacking. Immunohistochemistry studies performed on tophi show that perivascular localized mononuclear cells are CD68+,S100A8+, S100A9+, and

24F9-, representing freshly migrated monocytes/macrophages. In contrast, almost all CD68+ mono- and multinucleated cells arranged within granulomas are S100A8-, S100A9-, and 25F9+, representing mature (non migrating) macrophages. These macrophages coexpress TNF-α, and matric metalloproteinases (MMPs) ,2 and 9. In parallel, macrophages undergo apoptosis, a phenomenon that may restrict the destructive potential of inflammatory macrophages. Corticosteroids could enhance tophus formation, as shown in the air pouch model by rull and colleagues and in clinical reports.

IMAGING GOUT

Radiographic examination in patients who have gout is used mainly to evaluate joint destruction and disease presence of tophi, and to help exclude other diagnoses. Radiographic findings may be categorized into the nonspecific changes that are seen in early gout, the subtle alteration of intercritical gout, and the more specific changes of chronic tophaceous gout. In the early stage of gout, the radiographs usually are normal or show nonspecific soft tissue swelling in the affected joint secondary to synovitis, capsular disention, and periarticular soft tissue edema. As the attack subsides, the radiographic abnormalities usually disappear. Other causes of mono articular soft tissue swelling, including infection arthritis, pseudogout, and trauma, must be excluded. In the intercritical period, which occurs between the acute period and the development of chronic tophaceous gout, sutle joint alteration (eg. small, well-defined erosion) may be visualized at the periphery of affected joints

Characteristic findings occur in chronic gout. These include tophi, erosions with overhanging edges, relative preservation of the joint space, and lack of osteopenia. The hallmark of chronic gout is the presence of multiple macroscopic tophi a mixture of monosodium monohydrate crystals in a matrix of amorphous debris containing urate, proteinaceous deposits, and lipids with a surrounding foreign body reaction. Generally, they are

ovoid and asymmetric and usually are radio graphically invisible until they reach 5 mm to 10 mm in diameter. Large tophi may be palpable. Faint calcification may occur in up to 50 percent of tophi. However, cloud like masses of densely calcified tophi is atypical and may reflect a coexisting abnormality of calcium metabolism, such as renal insufficiency. Erosion in chronic gout is common and usually is associated closely with the tophaceous deposits because the erosion may occur secondary to chronic pressure from the adjacent tophus. When characteristic erosion is seen along with tophi the diagnosis of gout is almost certain. Frequently, these erosions are round or oval in shape and well circumscribed, and typically are eccentric and oriented along the axis of bone. Most often they are juxta-articular but may be intra articular or located at a distance form the joint. Intra-articular erosions tend to involve the joint margins before extending to the middle of the joint. Interosseous erosions may have sclerotic borders that produce a punched-out appearance.

A characteristic feature of gouty erosions is the overhanging edge, and elevated margin of bone that extends over the expected confines of the cortex at the site of erosion. The overhanging edge is seen in approximately 40percent of patients who have tophaceous gout and may represent new bone formation around a gradually enlarging tophus. Occasionally, extensive osseous erosions produce a mutilating arthritis that mimics the opera-glass hand deformity that is seen occasionally with rheumatoid or psoriatic arthritis.

The joint space is relatively well preserved, even in the presence of extensive juxta - articular erosions. Large tophi are an important radiographic feature the helps to differentiate gout form other causes of arthritis. If joint space narrowing has occurred, the radiographic appearance may mimic the uniform narrowing of rheumatoid arthritis or advanced osteoarthritis (OA). However, patient who have joint space narrowing generally have had long - standing disease and the clinical diagnosis of gout already is well established. Ankylosis with

obliteration of the joint space is rare. Osteopenia is an atypical feature of gout. When bone density is diminished in long-standing gouty arthritis, disuse is believed to be the cause & may be seen during an acute gouty attack, presumably from inflammation-induced hyperemia. However, this is transient and the bone density tends to be preserved, even in advanced chronic gout with articular destruction. In frequently, a zone of osteoporosis in the sub chondral bone may progress to a cystic abnormality. Interosseous tophi and sub chondral cysts may mimic focal osteoporosis and should not be confused with diffuse periaticular ostepenia.

Localized increase bone density may be seen in a minority of patients (-6percent) that has advance tophaceous gout, predominantly in the hands and feet. The increased bone density may represent calcification of interosseous monosodium urate deposits. The radio graphic appearance may resemble an area of bone infarction or enchondroma. Occasionally, bone proliferation is present in gouty arthritis. Enlargement of the ends and shafts of involved bones can produce club-shaped metatarsal and phalangeal heads. This is termed as“mushrooming.” Irregular bone spicules are noticed at the site of muscle /tendon insertion of the bones such as calcaneus, olecranon, and patella. A fine lacy periosteal new bone formation may form secondary to periosteal reaction that is caused by cortical destruction by adjacent crystal deposition, and often, this is best seen on the medial aspect of the first MTP joint. Bilateral olecranon bursitis is charactersitic feature of a gouty arthritis.

Hyperuricemic patient may present with urinary calculi before developing gouty arthritis. A non-contrast CT scan performed with thin slices (3-5 mm) through the urinary-collecting system has replaced intravenous urography as the gold standard for detecting urinary calculi, which can detect urate stones as small as 2 mm without much of difficulty. CT rarely is useful in patients who have gout other than for the detection of urinary calculi. Although several papers have described MRI findings in patients who have gout, MRI is not used as a

routine diagnostic tool.

TREATMENT

The therapeutic aims in gout are as follows:

- To terminate the acute attack as promptly and gently as possible.
- To prevent recurrences of acute gouty arthritis
- To prevent or reverse complications of the disease resulting from deposition of sodium urate or uric acid crystals in joints, kidney, or other sites.

- To prevent or reverse associated features of the illness that are deleterious, such a obesity, hypertriglycerdemia, and hypertension. The time of initiation of therapy is more important then the choice of drug. With any choice of drug. With any of these agents, the sooner the drug is started, the more rapidly a complete response will be attained generally, colchicine is preferred for patients in whom the diagnosis of gout is not confirmed, whereas NSAIDs are preferred when the diagnosis is secure. If a patient cannot take medications orally due to active peptic ulcer disease, the other options are intravenous colchicines, intra-articular glucocorticoid or parentral glucocorticoids. Local application of ice packs may help control the pain of an acute attack. In some cases, analgesics, including narcotics, may be added as well. The commonest cause of difficulty in controlling an attack is the simultaneous administration (or withdrawal) of drugs that alter the plasma urate concentration. Both increases and decreases in the plasma urate concentration may precipitate or prolong an attack of gout. Therefore, therapy aimed at reducing urate concentrations should be delayed until the complete resolution of all signs of inflammation. However, should the patient be stabilized on a constant dose of a urate - lowering drug at the time of an acute attack, the urate-lowering drug should be continued at the same dose until specific treatment has caused the acute gout to subside.

Colchicine

Colchicine is an alkaloid derived form the autumn crocus Colchicum autumn ale. It has an anti-inflammatory action in acute attacks of gout and a prophylactic effect against recurrent attacks. It has no effect on the serum urate concentration or on urate metabolism. Colchicine derives its effectiveness from its ability to interfere with acute inflammatory reactions in a variety of ways many of them mediated through the effects on neutrophil microtubules. Colchicine inhibits E-Selectin-mediated adhesiveness of neutrophils and diminishes neutrophil L-selection expression, random motility, chemotaxis, PLA activation, and IL - 1 expression, as well as the stimulated elaboration of PLAF (Platelet-activating factor) and the chemotatic factors CCF and LTB4. Colchicine also inhibits endothelial cell ICAM- expression, mast cell histamine release, and down regulates TNF-a receptors on macrophages and endothelial cells.

Colchicine can be administered by oral or intravenous routes

Orally, a dose of 0.5 or 0.6 mg is taken hourly until one of three things occurs: 1) Joint symptoms ease; 2) nausea, vomiting, or diarrhea develops; or 3) the patient has taken a maximum of 10 doses. If 10 doses are taken without benefit, the clinician should question the accuracy of the diagnosis. Peak plasma concentrations occur within 2 hours of oral administration. Although, the plasma half-life of colchicine is only 4 hours after oral administration, colchicine levels can be detected in neutrophils even 10 days after ingestion. Colchicine has a low therapeutic index with steady-state plasma concentration ranging between 0.5 and 3.0 ng/ml following an acute treatment. At the same time the toxic effects of colchicines can occur even at a concentration of 3 ng/ml. Therefore, in most patients, the side effects precede or coincide with improvement in joint symptoms. These side effects develop in 50 to 80 percent of patients and include increased peristalsis, cramping abdominal pain, diarrhea, nausea, or vomiting. The drug must be stopped promptly at the first sign of

gastrointestinal side effects.

Colchicine can also be given intravenously. When used properly, the drug abolishes the acute attack with a low incidence of gastrointestinal side effect (Provided that the patient is not also taking colchicines by mouth). An initial dose of 1 or 2 mg can be followed by one or two additional 1 -mg doses administered at 6 hour intervals, if needed. The total dose of intravenous colchicines should not exceed 4 mg. The colchicines should be diluted with 20ml of normal saline before administration and given slowly into an established venous access to minimize sclerosis of the vein.

In addition, oral colchicines should be discontinued and no additional colchicines should be given for at least 7 days because of the slow excretion of this drug.

The use of intravenous colchicines is associated with some risk. The most common complication is local extravasations during or immediately after injection. This can lead to inflammation and necrosis and may be extremely painful. The drug should not be given to patient who are neutropenic or to those with significant liver or renal disease. Although this form of therapy is effective, the reports of severe toxicity and death caused by inappropriate use of the medication are too plentiful.

Non steroidal anti-inflammatory drugs

In the patient with an established diagnosis of uncomplicated gout, the preferred agent of choice is an NSAID. Indomethacin has been the traditional choice of agents in this class. Although this drug may be effective in doses as low as 25 mg given four times a day, an initial dose of 50 to 75mg, followed by 50 mg every 6 to 8 hours with a maximum dose of 200mg in the first 24 hours, has generally been recommended. To prevent relapse, it is reasonable to

continue this does for an additional 24 hours, and then taper to 50 mg every 4 to 8 hours for the next 2 days. Clinical trials have also shown that oral naproxen, fenoprofen, ibuprofen, sulindac, piroxicam, and ketoprofen, as well as intramuscular ketorolac, are also effective. In fact all members of this family of drugs can be highly effective in the treatment of acute gouty arthritis, including the cyclooxygenase-2 (COX-2) selective agents.

Glucocorticoids

Intra-articular glucocorticoids are useful in the treatment of acute gout limited to a single joint or bursa. Oral glucocorticoid usage along with a single intramuscular or intravenous injection of a parentral glucocorticoid can also provide relief. Anecdotally, rebound attacks have been reported as steroids were withdrawn. ACTH has been used effectively, especially in attacks in patients following surgery.

Prophylaxis

The practice of giving small daily doses of colchicines as prophylaxis to prevent acute attacks up is proven to be effective. The use of colchicines at 0.6 mg once to three times a day is generally well tolerated, although the drug may produce a reversible axonal neuron myopathy. In patients who are unable to tolerate even one colchicine tablet per day, indomethacin or another NSAID can been used prophylactically at low doses (e.g., 25 indomethacin b.i.d) with some success. A program of maintenance with colchicines or a NSAID may make difference by avoiding frequent incapacitation and facilitating uninterrupted daily activities. Prophylaxis usually is continued until the serum urate levels have been maintained well with in the normal range and there have been no acute attacks for a period of 3 to 6 months. It is important to warn patients that discontinuation of colchicines may be followed by an exacerbation of acute gouty arthritis. Prophylactic colchicines may block the

acute inflammatory response but does not alter the deposition without of crystals in tissues.

With continued deposition without the warning signs of recurrent bout of acute arthritis, tophi and destruction to cartilage and bone can occur without notice.

Correction of the causes of hyperuricemia

Prevention of gout is directed at restoring the plasma urate concentration to normal. Many factors contributing to an elevation of urate concentration have been recognized and a number of these factors can be identified in individual patients with gout. Factors already identified as contributing to hyperuricemia include the syndrome of obesity, hypertriglyceridemia, hypertension and insulin resistance, which is an increasing public health and nutritional problem in western societies. Correction of obesity can cause remission of hyperuricemia and even a moderate loss of weight can facilitate the renal excretion of urate. However, the necessary changes in lifestyle and diet are rarely maintained long term, although increasing community recognition of the need to maintain a healthy lifestyle may help this in the future. In addition, diuretic therapy or inadequately treated hypertension will contribute to hyperuricemia.

A high purine intake will also contribute. Although, high purine foods are well-recognized contributors, it is less commonly appreciated that a large helping of a food with a medium concentration of purines may provides a much larger purine load than a small helping of a food high in purines. Moderation of purine intake and avoidance of high purine foods is desirable in most patients with gout, particularly if there is any difficulty in achieving a normal plasma urate.

Dietary restriction of purines rarely causes a fall in the plasma urate concentration of

more than 1.0 mg/dl (o.o6mmol/l) unless the diet has had large purine content. Moreover, such dietary restriction can rarely be sustained for long and is only occasionally clinically useful.

Antihyperuricemic drugs provide a definitive method for controlling hyperuricemia .In general the lower the serum urate level achieved during anti hyperuricemic therapy, the faster the reduction in tophaceous deposits. Reduction to target level may be achieved pharmacologically by the use of xanthine oxdase inhibitors or uricosuric agents. Once initiated, the use of antihyperuricemic agent is ordinarily carried on indefinitely for those patients with gout who excrete less than 800 mg of uric acid per day and have normal renal function. Reduction of serum urate concentration can be achieved equally well with a xanthine oxidase inhibitor or a uricosuric drug. These agents are equally effective n preventing deterioration of renal function in patients with primary gout. In most cases, allopurinol is probably the drug of choice because it can be used with fewer restriction compared to uricosuric agents.

In general, the candidate for uricosuric agents is the gouty patient who is younger than 60 years of age and has normal renal function uric acid excretion of less than 800 mg/24 hours on a general diet, and no history of renal calculi. Probenecid is readily absorbed from the gastrointestinal tact. Its half-life in plasma is dose dependent varying from 6 to 12 hours. This can be prolonged by the concomitant use of allopurinol.

The maintenance dosage of probenecid ranges from 500 mg to 3 g per day and is administered on a twice or three times a day schedule. Acute gouty attacks may accompany the initiation of this medication, as with medication, as with all other antihyperuricemic agents, and, as with all uricosuric agents, patients using probenecid are at increased risk for developing renal calculi Sulfinpyrazone is completely absorbed from the gastrointestinal tract and has a half-life of 1 to 3 hours. Most of the drug is excreted in the urine as the parahydroxylmetabolite, which is also uricosuric. Sulfinpyrazone is maintained at a daily dosed

300-400mg per day in three to four divided doses Benzbromarone is a potent uricosuric agent and can be used with moderate renal dysfunction. Patients' prescribed with uricosuric agent should be counseled to avoid salicylate use at doses greater than 81 mg per day.

In certain situations, an inhibitor of xanthine oxidase is clearly the drug of choice in the gouty patient. Gouty individuals who excrete larger quantities of uric acid in their urine or who have a history of renal calculi of any type should be treated with allopurinol. The incidence of renal calculi is about 35 percent in patients with primary gout who excrete more than 700 mg/day of uric acid. Allopurinol is converted to oxipurinol an inhibitor of xanthine oxidase. Allopurinol is metabolized in the liver and has a half-life of 1 to 3 hours, but oxipurinol, which is excreted in the urine, has a half-life of 12 to 17 hours. Because of these pharmacokinetic properties, allopurinol is dosed on a daily basis, and the dosage required to reduce serum urate levels is lower in patients with decreased glomerular filtration rates .Allopurinol should be used at the lowest dose that lower the serum urate level below 6 mg/dl. This most often achieved with doses of 300 mg per day, but a maximum of 800 mg can be used The sudden lowering of serum urate concentrations that accompanies initiation of allopurinol therapy may trigger acute gout attacks. This risk can be minimized by beginning prophylactic colchicines or NSAID two weeks before the first dose of allopurinol. As an alternative, allopurinol can be started at a dose of 100mg per day and increased by 100 mg increments on a weekly basis. Around 20 percent of patients who take allopurinol report side effects, with 5 percent of patents discontinuing the medication. The side effects are gastro intestinal intolerance, skin rash, alopecia, bone marrow suppression with leucopenia or thrombocytopenia, agranulocytosis, aplastic anemia, granulomatous hepatitis, jaundice, sarcoid like reaction, and vasculitis. Allopurinol will potentiate the action of other agents that are inactivated by xanthine oxidase, the most important of them are azathioprine and 6-mercaptopurine.

REVIEW OF LITERATURE

Epidemiologic data suggest that the overall disease burden of gout remains substantial and may be increasing. The national arthritis data work group reviewed earlier population based studies that estimated the prevalence of gout, such as Tecumseh community health study, the Framingham heart study and the Sudbury study. According to the most recent available national health interview survey (NHIS), data on self reported gout from the 1996 survey, the overall prevalence for the one year period was 9.4 cases per 1000persons in the United States. The prevalence increased with age from 1.8 per 1000 aged 18-44 to 33.5 per 1000 in persons aged 45-64 &46.4 per 1000 in persons aged 65 and older.

In the NHANES III (the national health &nutritional examination survey) the life time prevalence of gout was lowest (0.4%) in subjects aged 20-29, 11.6% in those aged 70 to 79. Although gout was reported more often in men than in women the overall prevalence in women approached that of men after menopause. The prevalence of gout was 3.2 percent in women aged 60 to 69 and increased to 5.2 percent in women aged 70 to 79 and 5.3 percent in women aged 80 years and older.

Data suggest that the prevalence of gout is increasing .Lawrence et al (5) reported a doubling of the prevalence. The steepest increase occurred between 1969 and 1976. Wallace et al (84) reported that the overall prevalence of gout and hyperuricemia requiring serum urate lowering medication had increased by 80 percent in 1999 as compared with that in 1990. Zeng et al (6) also reported a similarly increasing trend in Chinese population in 1990's.The Rochester Epidemiology project identified cases of new gout at an incidence rate of 45 per 1, 00,000 for the 2 year interval 1977 to 1978, which during the 1995-1996 was 62.3 per 1000, a greater than two fold increase in the rate of primary gout during the 20 year period. Choi et al

(7) reported increase in incidence and prevalence of primary gout with age in men and women. Aromadee et al (8) has reported a doubling in the incidence of primary gout in the past 20 years.

Campion et al (9) in the normative aging study evaluated the incidence of gout stratified by prior uric acid levels. Based on 84 incident cases of gout during a 15 year period, the all male study found the annual incidence of gout was less than 0.1 percent for men who had serum uric acid less than 7mg/dl, 0.4percent for 7-7.9mg/dl, 0.8percentfor 8-8.9mg/dl, 4.3percent for 9-9.9mg/dl and 7 percent for greater than 10mg/dl. Lin et al(10)studied men with hyperuricemia in a Chinese population for a 5 year period .42 cases of incident gout were documented .Annual incidence rates of gout in this study were 2.2percent for 7-7.9mg/dl , 5.5percent for 8-8.9mg/dl and 12.2 percent for greater than or equal to 9mg/dl. No data on the impact of prior uric acid levels on incident gout specifically in women are available. This study also showed significant associations with obesity, alcohol consumption and diuretic use for hypertension independent of uric acid levels. The study also found a significant interaction between persistent alcohol consumption and baseline uric acid levels in the hyperuricemic range.

Roubenoff et al (11) reported that increased BMI at age 35 but not at base line was associated with the risk of gout. Abbot et al (12) found a significantly higher BMI in patients who had gout after adjusting for age. Choi et al (14) compared men who had BMI 21-22.9kg/m, the multivariate RR of gout were 1.95(1.44-2.65) for men who had BMI 25 to29.9kg/m, 2.33(1.62-3.36) for 30 to 34.9kg/m and 2.97(1.73 -5.1) for greater than35kg/sq.m. The multivariate RR for gout in men in the highest waist to hip ratio quintile (0.98 -1.39) compared with those in the lowest (0.70-0.88) was 1.82(95 percent CI, 1.39-2.39). Emmerson et al (13) compared men who maintained their weight since age 21, the multivariate RR of gout

for men who gained 30 pounds or more was 1.99(1.49-2.66). In contrast the multivariate RR for men who lost 10 pounds or more was since the study baseline was 0.61.Increased adiposity leads to hyperuricemia via increased production and decreased renal excretion of urate.

Choi et al (14) reported increasing alcohol intake associated with increasing risk for gout (a dose response relationship).Compared with men who did not drink alcohol, the multivariate RR of gout increased from 1.25 for alcohol consumption to 2.53 (>50g/day).This risk varied substantially (5-9.9g/day) according to the type of alcohol beverage .Beer conferred a larger risk than liquor whereas moderate wine drinking did not increase the risk.

Graham et al (15) studied that the high prevalence of hypertension in patients who have classical gout is related more closely to obesity rather than the duration of gout. Prebis et al (16)states that renal uric acid clearance depends on the tubular secretory and post secretory reabsorption rates which was found to be lower relative to glomerular filtration rates in both the adult and childhood hypertensives and this correlated to the renal blood flow.

Messerli et al(17) in the study on serum uric acid in essential hypertension states that selectively increased renal and peripheral vascular resistance are documented in subjects who have essential hypertension with hyperuricemia raising the possibility that hyperuricemia is a consequence of early nephrosclerosis in patients who have essential hypertension. Kanellis et al (18) states that the urate stimulates monocyte chemoattactant protein-1 production in vascular smooth muscle via mitogen activated protein kinase and cyclooxygenase2. Mazzali et al (19) demonstrated an increase in juxtaglomerular renin content and decreased macula densa neuronal nitric oxidesynthase content, implicating the mediating systems in the regulation of blood pressure. The preglomerular arteriopathy accompanying these changes accounts for development of a salt sensitive hypertensive state, not reversible by lowering of serum urate levels.

Feig and Johnson et al (20) demonstrated a linear relationship between serum urate levels and systolic blood pressure in adolescents who have new onset hypertension .Segura et al (21) reported urate levels to correlate development of chronic renal insufficiency in patients who have hypertension. Leoncini et al (22) reported higher serum urate levels in those who have renal impairment. Johnson et al (23) supports the view that hyperuricemia is an important risk factor for ischemic heart disease and other forms of cardiovascular disease.

Brand et al predicted hyperuricemia as a risk factor for coronary artery disease .Nagahama et al(25) has reported clustering of hyperuricemia with cardiovascular risk factors .Fang J et al(26) reported increasing serum urate concentration was related to increasing cardiovascular mortality in both sexes and in blacks and whites.

Rich M Wet al (27) reported that serum urate levels >/=6 mg/dl were found to be an independent predictor of coronary artery disease. Hoieggen et al (28) in the LIFE study reported a significant association between baseline serum urate level and risk for a morbid or fatal cardiovascular event. The risks of recurrent coronary disease events were correlated

significantly with serum urate levels such that the serum urate was regarded as an independent predictor of recurrent coronary heart disease events. Mercuro et al (29) suggested that restoration of normal serum urate by allopurinol 300mg daily improves the flow mediated dilatation aspect of vascular function. Madsen et al (30) reported that higher serum urate levels are predictors of mortality in patients with significant angiographically defined coronary artery disease.

Lehto et al(31) found hyperuricemia as a predictor hazard of nonfatal and fatal stroke in a population based study of middle aged NIDDM. Mazza et al (32) in the CASTEL study (cardiovascular study in the elderly) reported serum urate as an independent predictor of stroke mortality, poor outcome and subsequent vascular events especially in diabetics. Abuja et al (33)studied that the levels of antioxidants such as ascorbate are reduced immediately after acute ischemic strokes .Patients who have the worst outcomes are those who have higher plasma urate levels raising the speculation that under circumstances of alternative antioxidant depletion urate may become pro oxidant.

Tseng et al (34)identified hypertension as a significant and independent risk factor for peripheral arterial disease in Taiwanese men who have type 2 diabetes mellitus and also for carotid atherosclerosis .Neuto et al (35) in their prospective case controlled study found baseline serum urate levels associated significantly and independently with increased coronary atherosclerosis(13 years later).

Hare et al (36)study suggests urate as a strong contributor to more severe heart failure through its role in hypertension. Capola et al (37) demonstrated evidence for direct and indirect pathophsiologic roles of abnormal urate metabolism in congestive heart failure. Ekelund et al (38) demonstrated that allopurinol decreases myocardial oxygen consumption. Ukai et al (39) reported that allopurinol improves systolic function in patients of congestive heart failure.

Doehner et al (40) proposed that endothelial damage resulting from xanthine oxidase generated oxygen free radicals as a basis of cardiac dysfunction in hyperuricemic states and allopurinol inhibition of xanthine oxidase is reported to improve endothelial dysfunction in patients who have heart failure.

Denzer et al (41) reported that serum urate levels contribute significantly to levels of HDL cholesterol, total cholesterol, BMI and systolic pressure in children and adults who are obese and may be a reliable marker of "Premetabolic syndrome". Vuorin –Markkola(42) found the inverse correlation of serum urate and insulin sensitivity and the positive correlation of urate and triglceride in 50 percent .Also suggested that hyperuricemia may be used as a simple marker of insulin resistance.

Emmerson et al (43) studied that weight reduction is associated with a modest lowering of serum urate concentration and decrease in rate of de novo purine biosynthesis. Dessein et al (44) stated that the weight loss associated with moderate calorie and carbohydrate restriction and increased proportional intake of protein and unsaturated fat is accompanied by a decrease in seum urate levels and dyslipidemia in patients who have gout. Tsunoda et al (45) has demonstrated amelioration of insulin resistance by a low energy diet that decreases serum urate levels in individuals who are hypertensive and overweight.

Donahue et al (46) found most obese persons to show leptin resistance and inceased leptin levels to be associated with leptin resistance in individuals who are non diabetic. Ruige et al (47) found that insulin response, triglceride levels and BMI to be independently and significantly associated with leptin concentration. Ogura et al (48) found correlation of serum urate and leptin in healthy male adolescent. Garcia et al (49) found the correlation of serum urate and leptin in moderately obese women.

Bedir et al (50) studied that creatinine, leptin insulin and triglceride levels accounted for the variability in serum urate in men and women. Serum urate, obesity and insulin resistance may be mediated atleast in part by leptin expression and that leptin levels may prove to be a link between obesity and hyperuricemia.

Daskalipoulou et al (51) reported that in humans fasting serum triglyceride may be the most important determinant of serum urate levels. Takahashi et al (52) found no association between gout and HDL levels or BMI suggesting that decreased HDL levels are attributed to altered triglyceride metabolism. Cardona et al (53) studied that the prevalence of apolipoproteinE2 allele was greater in patients who had gout and its presence was associated with higher triglyceride levels in very low density and intermediate density lipoprotein and with reduced renal uric acid excretion.

Yuorrin-Markkola et al (42) studied the relationship between hyperuricemia and insulin resistance and suggested that it might be indirect and mediated through fasting plasma triglyceride levels. Rocic et al (54) reported that in experimental animals urate suppresses basal insulin release and inhibits glucose stimulated insulin secretion. Facchini et al (55) in a study of the relationship of insulin mediated glucose disposal and serum urate in 36 healthy non diabetic volunteers found renal uric acid clearance to be reduced in proportion to increased insulin resistance resulting in increased serum urate concentration. Yuorrin-Markkola et al also reported the association between hyperinsulinemia and reduced uric acid clearance.

Lin and Chou et al (56) studied that persistent hyperuricemia in postmenopausal state is associated with subsequent development of diabetes. Nakanishi et al (57) in a longitudinal study on Japanese male office workers found the strong association between serum urate and hypertension and /or type2 diabetes mellitus. The relationship with diabetes was stronger in men who had a BMI of less than 24kg/m compared with higher BMI but the absolute risk was

greater in more men who were obese. Gockcel et al (58) reported that metformin administered not only reduces post prandial and fasting blood glucose levels but also serum urate levels.

LiuBryan et al (59) have described toll like receptorTLR2 andTLR4 on the cell surface which has been implicated in chondrocyte and macrophage signaling. Murakami et al(60) reported that monosodium urate crystals could induce rapidly on neutrophils the expression of trigerring receptors expressed on myeloid ce4lls(TREM).Ryckman et al(61) identified factors like meloid related protein in the mediation of acute monosodium urate crystal induced inflammation.

Tramoniti et al (62) identified complement membrane attack complex as the mediator of acute attack. Inokuchi et al (63) reported IL-8 to be increased in the plasma from patients who have gouty arthritis which was secreted by monocytes after monosodium urate crystal stimulation along with an activation of caspase-1 the processing enzyme for IL-8 activation. Neutrophil apoptosis is advocated as a possible mechanism for resolution of an acute attack. Huyn and Fadok et al (64) stated that apoptotic cell recognition and clearance via exposure of phosphatidylserine and ligation of its receptor induce TGF B secretion resulting in acclerated resolution of inflammation.

Pascal et al (65) identified monosodium urate crystals in synovial fluid taken from the first metatarsal or knee joint of asymtomatic patients with proven gout during the intercritical period. He also reported that treatment with colchicine decreases white cell counts in the synovial fluid of asymptomatic knee that contain monosodium urate crystals. Liu et al (66) studied that chondrocytes can phagocytose particles and in vitro non adherent chondrocytes can produce active MMP, S after monosodium urate crystal stimulation.

Liu Bryan(67) et al studied that direct chondrocyte cell membrane crystal can trigger

cell activation ,NO synthase expression and NO production,IL-1B activation and MMP expression which can contribute to cartilage degradation and further tophus breaking. Bouchard et al (68) reported that monosodium urate crystals contribute to bone lesions and MSU crystals reduce the activity of osteoblasts in vitro thereby limiting the healing process of erosions.

Vandiver et al (69) observed that defect in anti-inflammatory properties of macrophages could contribute to low grade inflammation by residual MSU crystals. LiotiF et al(70) has identified ultrasound as a promising new modality for gout. Koski et al (71) reported the frequent finding of small fluid collections in the first MTP joints. Thiele and Schleisinger et al (72) in a study of 23 patients of gout found ultrasound to detect early gouty erosion. They also demonstrated the sensitivity of ultrasound in the detection of calcification of hyaline articular cartilage.

Becker et al (73)in a recent study of 762 patients of gout compared the effects of allopurinol(300 mg daily) with febuxostat a new xanthine oxidase inhibitor(80mg & 120 mg).The primary end point (a serum urate <6mg/dl)was achieved in only 21 percent of the patients receiving allopurinol compared with 53 percent of the patients receiving 80mg of febuxostat and 62 percent of those receiving 120mg/day of feboxostat .He also reported that febuxostat is safe and effective in lowering serum uric acid levels in patients who have gout and hyperuricemia, safe and more effective in maintaining serum urate levels.

Wortman (74) et al reported that febuxostat is more effective in reducing the size of tophi during 12 months. Moolenberg et al (75) has reported that rasburicase given by repeated intravenous injection had good effect in cases of tophaceous gout resistant to combined treatment with allopurinol and benzobromarone. Sundy et al (76) in an open labeled phase 2 study found that use of multiple intravenous injections of PEG uricase in severe refractory gout confirmed sustained and substantial reduction of serum urate. Baraf (77) et al observed rapid resolution of tophi within three months in two patients following PEG uricase therapy.

AIM OF THE STUDY

- To study the epidemiological characteristics of various patients of gout.
- To study the musculoskeletal features and biochemical characteristics in them.
- To analyze the comorbidities in these patients.

MATERIALS

Seventy consecutive patients of gout who attended the department of rheumatology, Madras Medical College were included in the study.

This is a Prospective Study conducted between January 2006 and March 2008.

INCLUSION CRITERIA

A definitive diagnosis of gout was established by demonstration of intracellular uric acid crystals in the synovial fluid or tophi. When crystals could not be demonstrated diagnosis was established if six of the twelve American rheumatism association (ACR) criteria were fulfilled.

EXCLUSION CRITERIA

Patients of psoriasis, Systemic lupus erythematosus and hematological malignancies with elevated uric acid levels were excluded from the study.

METHODS

All patients were asked for a detailed history which includes the duration of the disease, disease onset, the first joint affected, the duration of the attack, the time interval between subsequent episodes, whether it was a persistent arthritis, and time of onset of first MTP joint involvement .A history of other illnesses such as coronary artery disease, hypertension, hypothyroidism and consumption of alcohol was asked for. A detailed general examination, height, weight and body mass index was calculated. A musculoskeletal system examination and other systems were done.

Hematological evaluation included complete hemogram and peripheral

smear. Biochemical parameters including blood glucose, urea, serum creatinine, liver function test, fasting lipid profile, serum uric acid, 24 hour urinary uric acid excretion and synovial fluid analysis for monosodium urate crystals were done.

Ultrasound of abdomen was done with reference to fatty liver, renal abnormalities, renal calculi, renal cyst, and features of medical renal disease. USG assessment of Intimomedial thickness of the carotid arteries was done in 50 patients. Plain x-rays of the involved joints were taken. CT scan of the feet was done in four patients and hands done in one.

RESULTS

AGE & SEX

Seventy patients of gout were analyzed of which 57 were males and 13 were females. Five patients belonged to the group of young onset gout (< 30 Yrs) and all of them were males. The mean age of patients of young onset was 25.3 ± 5.08 yrs. with a 't' value of 4.966 which was of high statistical significance. The mean age of males in late onset group was 45.32 ± 11.65 yrs. and females was 48 ± 7.93 yrs. There was no statistically significant difference in age distribution among sexes (t value of 0.788). 38 patients (55.5%) gave history of alcohol consumption, of which 37 are males.

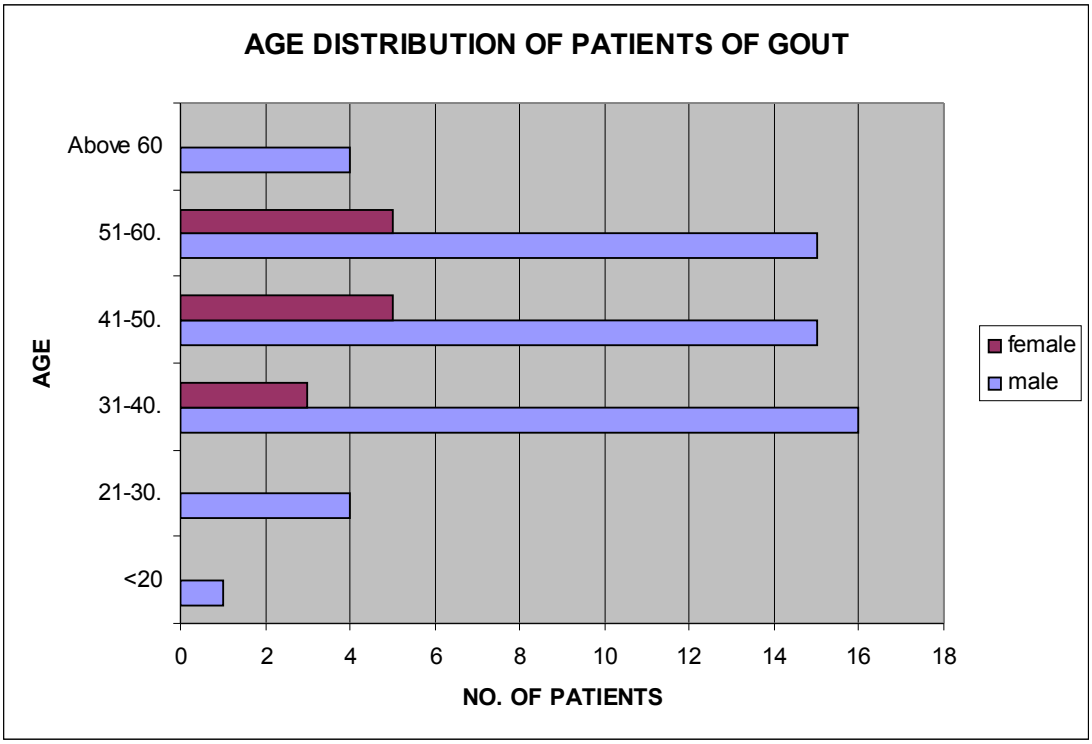


TABLE 1: MEAN AGE OF PATIENTS OF GOUT

Age	Male (Age in yrs)	Female (Age in yrs)	Total (Age in Yrs)
Young <30 yrs	25.4±5.08	0	25±5.08
Adult >31	47.23±10.22	48±7.93	47.38±9.75
Total	45.32±11.65	48±7.93	

TABLE 2: FEMALES IN COMPARISON TO MALES

	Males	Females
Number of patients	57(81.4%)	13(18.6%)
Age in yrs	45.32±11.65	48±7.93
Duration in yrs.	4.36±4.01	2.08±1.43
Pattern of arthritis		
Polyarthritis	43(75.4%)	9(69.23%)
Oligoarthritis	13(22.82%)	4(30.77%)
Bursitis	1(1.75%)	0
1st MTP	48(84.2%)	8(61.5%)
Tophi	18(31.57%)	2(15.4%)
Hypertension	35(61.4%)	8(61.5%)
Diabetes Mellitus	4(7%)	2(15.3%)
Coronary Artery diseases	7(12.3%)	1(7.7%)
Hypothyroidism	2(3.5%)	6(46.1%)
S.Uric acid (mg/dl)	9.95±2.18	8.29±1.42
Hyper cholesterolemia	23(40.35%)	8(61.53%)
Hyper triglyceridemia	2(3.5%)	0
Both Hyper cholesterolemia, Hyper triglyceridemia	11(19.3%)	5(38.5.%)
S. Creatinine (mg/dl)	1.4±0.88	1.34±0.61

MUSCULOSKELETAL FEATURES

Polyarticular pattern was seen in 52 patients, (43 males and 9 females). Oligoarticular arthritis was seen in 17 patients (13 males and 4 females). The first joint affected was 1st MTP in 31 patients, knee joints in 21 patients ,small joints of hands in 9, ankle in 4, tarsal in 3,elbows in 1. One patient had bursitis of the foot (lateral malleolus) as the sole musculoskeletal manifestation. First metatarsophalangeal joint involvement was seen in 56 patients. 20 patients had tophi out of which 18 were men and 2 were women.

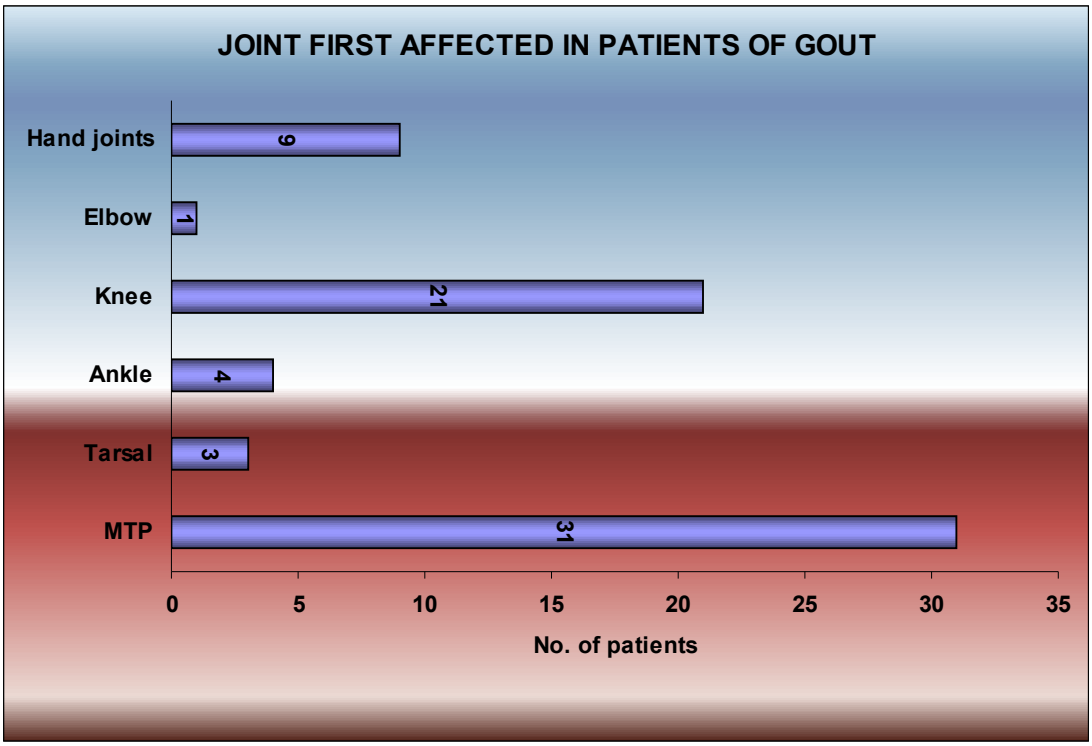


TABLE 3: COMPARISON OF OLIGOARTICULAR AND POLYARTICULAR GOUT

	Polyarticular	**Oligoarticular**
Number of patients	52(74.28%)	17(24.28%)
Age in Yrs.	47.01±11.81	42.29±7.98
Duration in yrs	4.49±3.99	2.43±2.54
Males	43(82.69%)	13(76.5%)
Females	9(17.3%)	4(23.52%)
Tophi	18(34.6%)	2(11.7%)
Hypertension	30(57.69%)	12(70.58%)
Diabetes Mellitus	5(9.6%)	1(5.8%)
Coronary Artery diseases	7(13.5%)	1(5.8%)
Renal failure	9(17.3%)	0
Hypothyroidism	5(9.6%)	3(17.6%)
S.Uric acid(mg/dl)	10±2.31	8.48±1.05
Hyper cholesterolemia	20(38.5%)	10(58.8%)
Hyper triglyceridemia	2(3.84%)	0
Both Hyper cholesterolemia, Hyper triglyceridemia	15(28.84%)	1(5.8%)

TABLE 4: TOPHACEOUS AND NONTOPHACEOUS GOUT

	TOPHACEOUS GOUT	NON TOPHACEOUS GOUT
No. of patients	20	50
Serum uric acid (mg/dl)	10.95±2.02	9.12±1.99
Pattern of arthritis	Polyarthritis 18 (90%) Oligoarthritis 2(10%)	Polyarthritis 34 (68%) Oligoarthritis 15(30%) Bursitis 1(2%)
Hypertension	11 (55%)	32 (64%)
Diabetes mellitus	2(10%)	4(8%)
Hypothyroidism	1(5%)	7(14%)
Renal failure	4 (20%)	5 (10%)
Dyslipidemia	12 (60 %)	37 (74%)
24 hours uricacid excretion(mg/day)	692.8±118.88	628.18 ± 179.81

COMORBIDITIES

1. Hypertension

Hypertension was found in 43 patients out of which 34 had dyslipidemia (27 males and 7 females).Among the 34 patients hypercholesterolemia was observed in 18,(14 males,4 females), hypertriglyceridemia in 2 males and both cholesterol and triglyceride were elevated in 14 (11 males,3 females).

2. Diabetes mellitus

Diabetes mellitus was present in 6 patients(8.5%),4 males and 2 females ,5 had hypertension, dyslipidemia was present in all, coronary artery disease in 3, renal failure in 2.

3. CAD, hypothyrodism, Renal failure

Coronary artery disease was present in 8 patients(7 males and 1 female). Hypothyroidism was documented in 8 patients (6 females and 2 males). Renal failure was present in 9 patients of which 6 are males and 3 are females.

4. Dyslipidemia

Dyslipidemia was present in 49 patients of which hypercholesterolemia was noticed in 31 patients (23 males and 8 females) & hypertriglyceridemia in 2 males. Both cholesterol and triglyceride were elevated in 16 patients (11males and 5 females).

5. Obesity

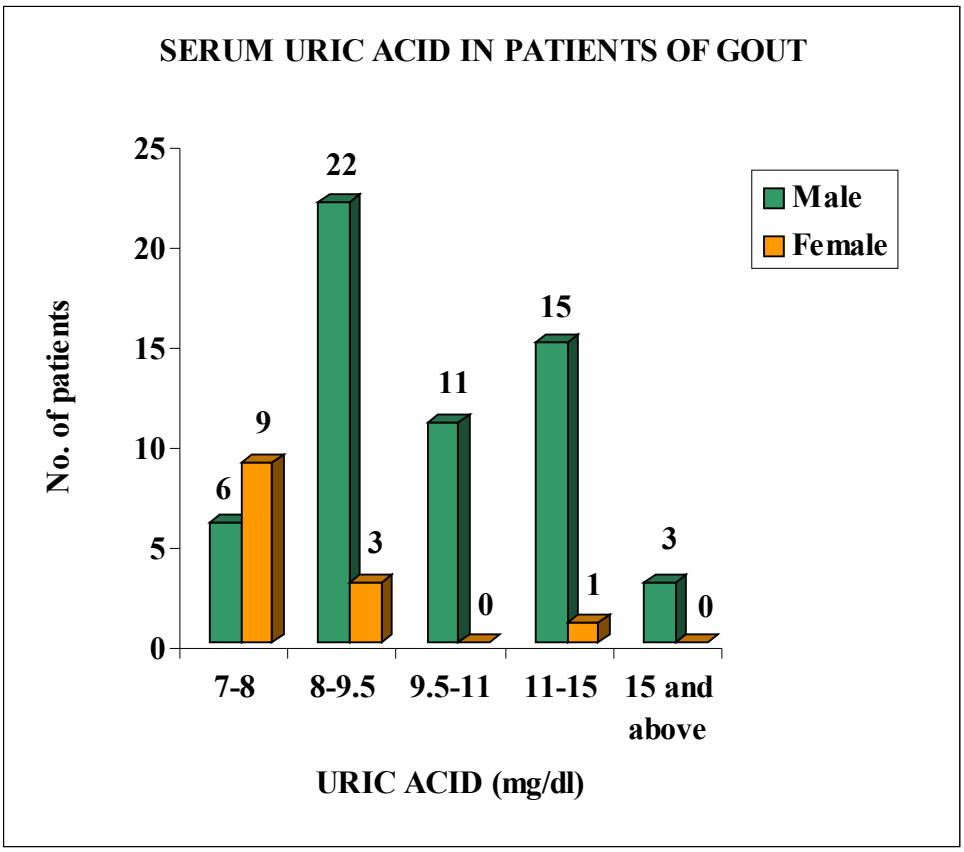
Obesity (BMI more than 25 Kg/m^2) was observed in 28 (40%) patients 21 males and 7 females.

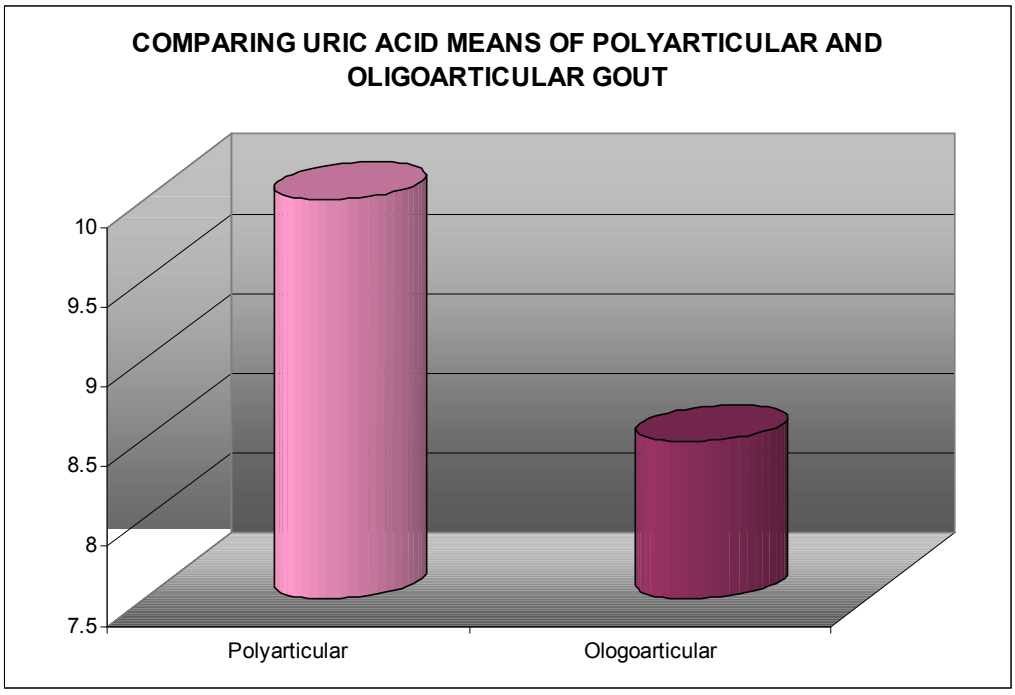
TABLE 5: HYPERTENSIVE AND NON HYPERTENSIVE GOUT

	Hypertensive	Non-hypertensive
Number of patients	43 (61.4%)	27(38.57%)
Age in yrs	48.8±11.2	40.96±9.19
Duration in yrs	3.52±3.51	4.61±4.12
Polyarthritis	30(69.76%)	22(81.4%)
Oligoarthritis	12(27.9%)	5(18.6%)
Bursitis	1(2.3%)	0
Tophi	11(25.6%)	9(33.3%)
Diabetes Mellitus	5(11.6%)	1(3.7%)
Coronary Artery diseases	7(16.2%)	1(3.7%)
Renal failure	8(18.6%)	1(3.7%)
Hypothyroidism	6(13.9%)	2(7.4%)
S.Uric acid(mg/dl)	9.87±2.37	9.27±1.73
Hyper cholesterolemia	18(41.8%)	13(48.14%)
Hyper triglyceridemia	2(4.65%)	0
Both Hyper cholesterolemia, Hyper triglyceridemia	14(32.6%)	2(7.4%)

LAB INVESTIGATION

The mean ESR was 30 ± 12 mm/hr. The serum uric acid values ranged from 7mg/dl to 17.2mg/dl. 15 patients had uric acid levels between 7 and 8 mg/dl(6males,9 females),25 patients (22 males ,3 females) had uric acid levels between 8 and 9.5mg/dl,11 patients had values between 9 and 11.5 mg/dl(all males), 16 patients with values between 11 and 15 mg/dl. All the 3 patients with serum uric acid values more than 15mg/dl were males.13 patients were over excretors of uric acid (>700 mg/day),2 had values >1000mg/day.CRP was elevated in 60 patients(85%).Rheumatoid factor was present in 2 patients. Proteinuria was present in 14(20%) patients.


SERUM URIC ACID IN PATIENTS OF GOUT
No. of patients
25
20
15
10
5
0
6
9
22
3
11
0
15
1
3
0
Male
Female
7-8
8-9.5
9.5-11
11-15
15 and above
URIC ACID (mg/dl)


COMPARING URIC ACID MEANS OF POLYARTICULAR AND OLIGOARTICULAR GOUT
10
9.5
9
8.5
8
7.5
Polyarticular
Ologoarticular

RADIOLOGY

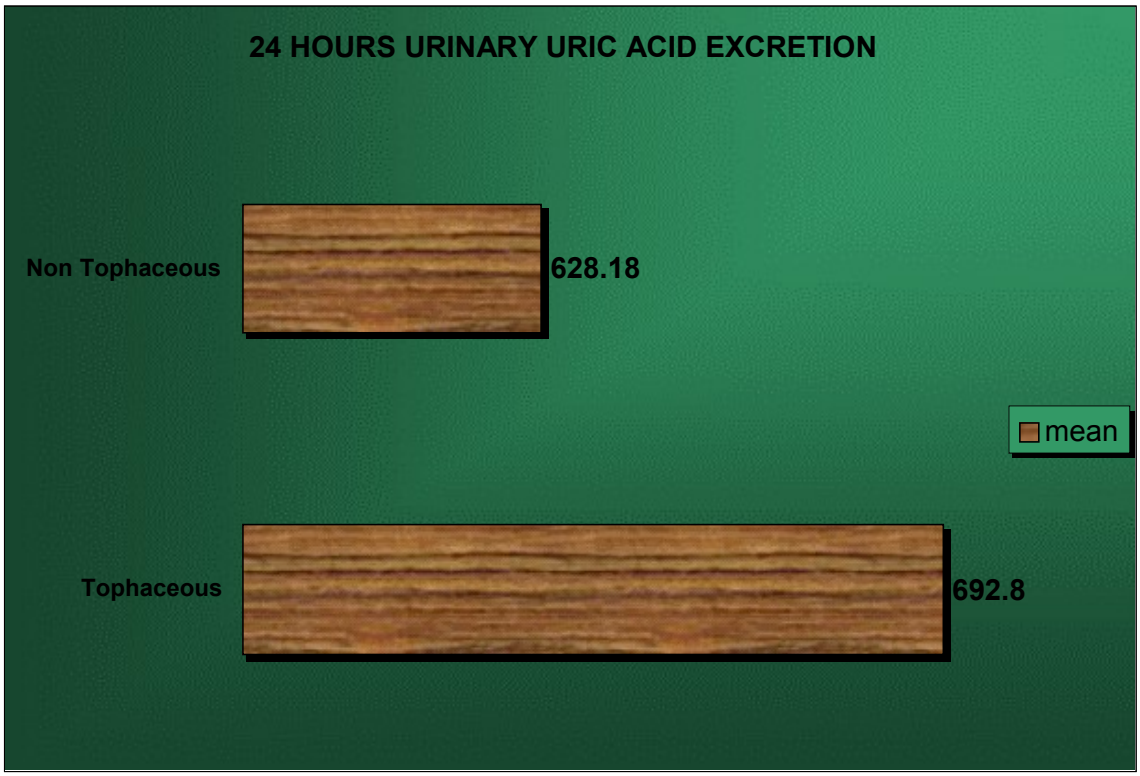
All the 20 patients of tophaceous gout had radiological evidence of tophi and erosions of the first MTP joint.

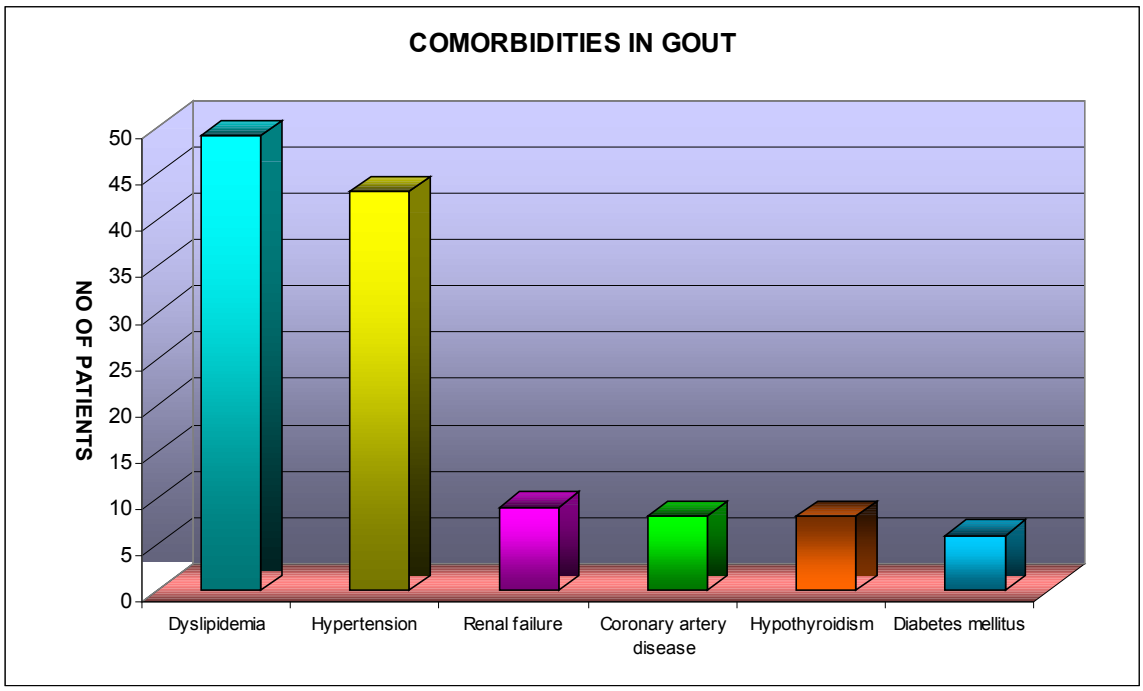
CT of the feet was done in 4 patients. It was normal in two patients. The third patients had erosion of the 1st MTP joint with tophus . The fourth patient had degenerative changes in the tibiotalar joint. CT of hands done in one patient showed tophi with destructive arthritis of the proximal interphalangeal joints.

Avascular necrosis was observed in 2 patients, left femoral head in one and right tibial lateral condyle in the other.

Renal calculi were present in 5(7.2%) patients. Renal cystic disease was seen in 3 patients. 9 patients had renal failure out of which 6 showed significant changes in the USG. Fatty liver were present in 31(44.3%) patients.

Intimomedial thickness of carotid arteries was assessed in 50 patients. Increased thickness was observed in 5 patients. All of them were hypertensive and dyslipidemic with serum uric acid levels were more than 10mg/dl. 4 patients (80%) had renal failure.


24 HOURS URINARY URIC ACID EXCRETION
Non Tophaceous
628.18
mean
Tophaceous
692.8


COMORBIDITIES IN GOUT
NO OF PATIENTS
0
5
10
15
20
25
30
35
40
45
50
Dyslipidemia
Hypertension
Renal failure
Coronary artery disease
Hypothyroidism
Diabetes mellitus

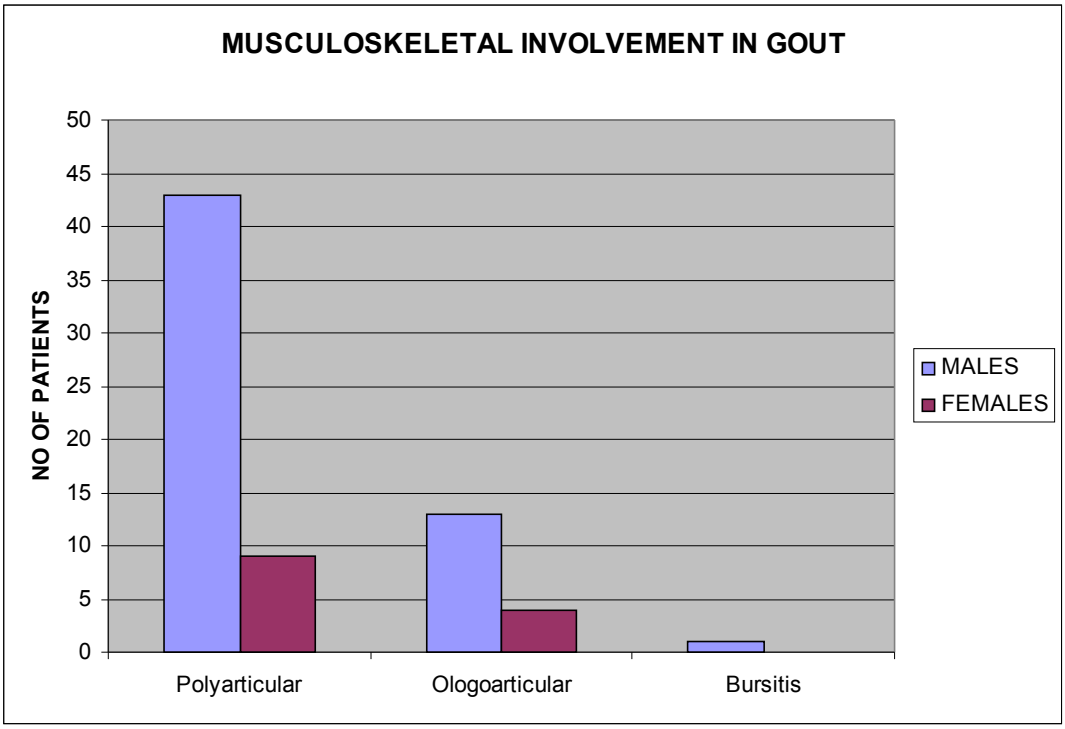
DISCUSSION

The mean age of onset in our study was 45.81+/-11.05 yrs which was comparable to other studies like Porkodi et al (86) 40.02yrs, Kumar et al (78) 45yrs & Gupta et al(79) 45yrs.Majority of our patients (84.3%) belong to the age group between 31 and 60 years whereas 7.3% belong to the Young onset group. Danda et al (87) had reported that 17.9% of the patients in his study belong to young onset group. There was no statistically significant difference in the serum uric acid levels between the patients of Young onset group and Classical gout.

The male to female ratio was 57:13in our study whereas in the study of Porkodi et al the female population was comparatively lesser (95:6). The mean age & duration of the disease were almost the same in both the sexes. The mean serum uric acid levels were higher in the males (9.95+/-2.18 mg/dl) than females (8.29+/-1.42 mg/dl). Similar findings were noted in the study of Porkodi et al with significantly higher serum uric acid levels in males (10.35) as compared to females (8.42 mg/dl). The predominant pattern of arthritis in our study in both the sexes was polyarticular (75.43% of males and 69.23% of females).In Porkodi et al study, the polyarticular pattern was commoner in females(66.7%) and oligoarticular pattern was predominantly seen in males(80%).The relationship between the sex and pattern of arthritis has not been widely discussed in the literature. The serum uric acid levels were higher in polyarticular group and the difference is statistically significant (p value<0.016). All the patients with renal failure (9 patients) had polyarthritis. Hyperuricaemia in renal failure is due to the reduced uric acid secretion.

Primary hyperuricaemia in renal disease due to reduced renal uric acid output is well documented in the literature. There could be an indirect relationship between polyarthritis and renal failure, because of higher serum uric acid levels. In our study we have found that there is a significant relationship between the serum uric levels and higher serum creatinine levels. Proteinuria was seen in 20% of patients. Fessel J et al(80) has reported a 20-40% prevalence of proteinuria which is usually mild and intermittent. Nephrolithiasis was present in 5 (7.2%) of patients. Yu T F et al (91) reported a 10-25% prevalence of the same in patients with primary gout. Hoyosa et al (92) found that 24-36% of patients of polycystic kidney disease develop gouty arthritis. We had a patient of gouty arthritis with polycystic kidney disease and renal failure.

Polyarthritis was common in both tophaceous and non tophaceous group in our study. The 24 hour uric acid excretion was significantly higher in the tophaceous than non tophaceous group (p value<0.016). This does not seem to explain the higher prevalence of polyarthritis pattern in the tophaceous group. All 20 patients of tophaceous gout had erosions of 1st MTP joint. Erosions in chronic gout are common and usually are associated closely with tophaceous deposits. These erosions occur secondary to chronic pressure from the adjacent tophi. There was one patient with bursitis (1.4%) as the only musculoskeletal manifestation. Rheumatoid factor was positive in 2(2.8%) patients. Wallace et al (84)in his study reported that 10% of gouty patients were positive for rheumatoid factor. Kozin et al (85) found that one third of patients of tophaceous gout had rheumatoid factor positivity.



The most common co morbidities in our study was hypertension .The other common co morbidities were obesity, coronary heart disease hypothyroidism & renal failure.

The prevalence of hypertension was almost equal in both the sexes. Poly arthritis pattern was the predominant pattern in majority of the hypertensive patients and there was no significant difference in serum uric acid levels between the hypertensive and non hypertensive patients in our study. Porkodi et al and Johnson RJ has stated a positive relationship between hyperuricemia and hypertension.

Majority of the patients with dyslipidemia were having high serum cholesterol levels and only 2 had higher triglyceride levels and some of them had both the cholesterol and triglyceride levels elevated. There was no correlation between serum cholesterol and serum uric acid levels in our study.

Scott J et al (81) in his study also concluded the same in his study. Many studies have concluded the direct relationship between hyperuricaemia and dyslipidemia, obesity and to their potential adverse effects.

Coronary heart disease was an important co morbidity seen in 11.4% patients in our study. Alderman et al reported that hyperuricemia is an important risk factor for ischemic heart disease. Nagahama et al (25) has reported the clustering of hyperuricemia with cardiovascular factors. The National health and Nutrition examination survey (NHANES) is a population based cross sectional study conducted to determine the risk of elevated serum uric acid levels in cardiovascular mortality. The study concluded that high serum uric acid levels has a significant risk of cardiovascular mortality. In our study, we found that serum uric acid levels to be relatively higher in the patients with coronary heart disease. Intimomedial thickness was also found to be increased in 3 of these patients. Five out of fifty patients in our study were found to have increased Intimomedial thickness. All the five patients were hypertensive and hyperlipidemic with serum uric acid levels more than 10mg/dl.

A significant co relation between hypothyroidism and defective purine metabolism and hyperuricemia has been noted in the past literature. The cause for hyperuricemia in hypothyroidism is due to reduced renal plasma flow and impaired glomerular filtration. All our patients with hypothyroidism in our study have relatively higher mean serum uric acid levels. Erickson AR(93) has reported increased prevalence of hypothyroidism in patients with gouty arthritis as compared to the control group. In the study of Erickson et al,

hypothyroidism was prevalent in 15% of patients of gout in 25% of females and 12% of males (a 2.5 times greater prevalence in women and 6 times greater prevalence in men than normal population).

Diabetes mellitus was present in 8.57 %(6) of patients in our study. Umber et al (89) reported a 5.4% prevalence of diabetes in gouty patients. Whitehouse and Cleary(90) found diabetes in 18% patients of gout as compared to 19% in controls. Bakowitz (88) reported a correlation between hyperuricemia and hypertriglyceridemia and an association of hypertriglyceridemia with decreased glucose tolerance. In our study 5(83%) patients of gouty diabetics had hypercholesterolemia and 50% had hypertriglyceridemia.

AVN has been reported in hyperuricemia of renal failure of post transplant patients. In our study one had AVN of the head of femur and the other had in the lateral tibial condyle. Mc Collum et al (83) in his study of AVN and associated diseases found an association of gout with AVN.

CONCLUSIONS

- Majority of the patients (79%) of gout in our study belonged to the age group of 31-60 years .
- Predominant pattern of arthritis was polyarticular.
- Five patients in our study belong to the Young onset group.
- Dyslipidemia and Hypertension were the common co morbidities in the male population.
- Hypertension, Dyslipidemia and Hypothyroidism were the common co morbidities in our female patients.
- A strong association between polyarticular gout and renal failure was noticed.
- Serum uric acid levels were higher in males than females.
- There was a significant correlation between uric acid levels and serum creatinine.
- The 24 hours uric acid excretion was higher in tophaceous gout than the non tophaceous gout.

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ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AVN	avascular necrosis
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CIA	crystal induced arthritis
CRP	C reactive protein
DM	diabetes mellitus
HTN	hypertension
LTB	leukotriene B
ICAM	inter cellular adhesion molecule
IMT	intimimedial thickness
IL	interleukin
HTN	hypertension
MSU	monosodium urate
MMP	matrix metalloproteinase
NO	Nitric oxide
MTP	metatarsophalangeal
RF	Rheumatoid factor
RR	relative risk
TGF	Transforming growth factor
TLR	Toll like receptor
TNF	Tumour necrosis factor
USG	Ultrasonogram

CRITERIA FOR THE CLASSIFICATION FOR ACUTE GOUTY ARTHRITIS

The presence of characteristics urate crystals in the joint fluid, or a tophus proved to contain urate crystals by chemical means or polarized light microscopy, or the presence of 6 of the following 12 clinical, laboratory, and radiographic phenomena:

I. More than one attack of acute arthritis

II. Maximal inflammation developed within 1 day

III. Attack of monarticular arthritis

IV. Joint redness observed

V. First metatarsophalangeal joint painful or swollen

VI. Unilateral attack involving first metatarsophalangeal joint.

VII. Unilateral attack involving tarsal joint

VIII. Suspected tophus

IX. Hyperuricemia

X. Asymmetric swelling within a joint (radiograph)

XI. Subcortical cysts without erosions (radiograph)

XII. Negative culture of joint fluid for microorganisms during attack of joint inflammation.

PROFORMA

NAME

Age Sex

Occupation Address

Duration of disease

Present history

Joints involved first

Joints involved later

Number of previous episodes

Pain and swelling of 1st MTP joint

Pain swelling of any other soft tissues

Past history

CAD

Hypothyroidism

Hypertension

Drug history

Low dose aspirin

Diuretics others

Personal history

Smoking

Alcohol

Tobacco chewing

Family history

Examination

Height Weight Skin Tophi Goitre

Cardiovascular system

Respiratory system

Abdomen

CNS

Musculoskeletal System

Joint	(R)W	(R)S	(R)T	(R)L	(L)W	(L)S	(L)T	(L)L
PIP								
MCP								
WRIST								
ELBOW								
SHOULDER								
KNEE								
ANKLE								
MTP								
IP								
HIP								
BURSITIS								
OTHERS								

INVESTIGATIONS

Hemoglobin

TC

DC

ESR

PLATELET

Urine routine

Urea

Creatinine

SGOT

SGPT

Cholesterol

Triglyceride

HDL

LDL

S.Uricacid

24 hour uric acid

T3 ,T4,TSH

RF

CRP

XRAY

USG ABDOMEN

IMT CAROTIDS ECHO

CT

APPENDIX 3

PATIENT CONSENT FORM

STUDY TITLE:

EPIDEMIOLOGY CLINICAL FEATURES AND COMORBIDITIES IN GOUT

Study Centre : Department of Rheumatology,Government General Hospital,Chennai.
Patient's Name : _____
Patinet's Age : _____
Identification Number : _____

Patients may check (✓) these Boxes

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that the investigator, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current tsudy and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identify will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any detorieration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby agree to allow the investigator to take around 30ml of blood from me for the laboratory investigations until the completion of study. ☐

I hereby give permission to undergo complete physical examination, and diagnostic tests including hematological, Biochemical, Radiological and urine examination. ☐

Signature / Thumb Impression of the patient. _____ Place _____ Date

Patient's Name&Address : _____
_____

Signature of the Investigator : _____ Place _____ Date
Study Investigator's Name : _____

INSTITUTIONAL ETHICAL COMMITTEE

GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE
CHENNAI.600 003

Telephone : 044 – 2530 5000
FAX : 044 - 2530 5115

K.Dis.No.25406/P&D3/Ethics/Dean/GGH/07 **Dated: 22.11.2007**

Title of the work : A Study of Gouty Arthritis

Principal investigator : Dr. R. Kirthi M.D.

Department : Dept. of Rheumatology.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 22.11.2007 at the Conference Hall of the Dean, Tower Block I, Government General Hospital, Chennai.3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their team are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s).
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH, Chennai.

CHAIRMAN
IEC, GGH, Chennai.

DEAN
GGH&MMC, Chennai.