

= Gout =

Gout is usually characterized by recurrent attacks of inflammatory arthritis ? a red , tender , hot , and swollen joint . Pain typically comes on rapidly in less than twelve hours . The joint at the base of the big toe is affected in about half of cases . It may also result in tophi , kidney stones , or urate nephropathy .

The cause is a combination of diet and genetic factors . It occurs more commonly in those who eat a lot of meat , drink a lot of beer , or are overweight . The underlying mechanism involves elevated levels of uric acid in the blood . At high levels , the uric acid crystallizes and the crystals deposit in joints , tendons and surrounding tissues , an attack of gout occurs . Diagnosis may be confirmed by seeing the crystals in joint fluid or tophus . Blood uric acid levels may be normal during an attack .

Treatment with nonsteroidal anti @@ inflammatory drugs (NSAIDs) , steroids , or colchicine improves symptoms . Once the acute attack subsides , levels of uric acid can be lowered via lifestyle changes and in those with frequent attacks , allopurinol or probenecid provides long @@ term prevention . Taking vitamin C and eating a diet high in low fat dairy products may be preventive .

Gout affects about 1 to 2 % of the Western population at some point in their lives . It has become more common in recent decades . This is believed to be due to increasing risk factors in the population , such as metabolic syndrome , longer life expectancy and changes in diet . Older males are most commonly affected . Gout was historically known as " the disease of kings " or " rich man 's disease " . It has been recognized at least since the time of the ancient Egyptians .

= = Signs and symptoms = =

Gout can present in multiple ways , although the most usual is a recurrent attack of acute inflammatory arthritis (a red , tender , hot , swollen joint) . The metatarsal @@ phalangeal joint at the base of the big toe is affected most often , accounting for half of cases . Other joints , such as the heels , knees , wrists and fingers , may also be affected . Joint pain usually begins over 2 ? 4 hours and during the night . This is mainly due to lower body temperature . Other symptoms may rarely occur along with the joint pain , including fatigue and a high fever .

Long @@ standing elevated uric acid levels (hyperuricemia) may result in other symptoms , including hard , painless deposits of uric acid crystals known as tophi . Extensive tophi may lead to chronic arthritis due to bone erosion . Elevated levels of uric acid may also lead to crystals precipitating in the kidneys , resulting in stone formation and subsequent urate nephropathy .

= = Cause = =

The crystallization of uric acid , often related to relatively high levels in the blood , is the underlying cause of gout . This can occur because diet , genetic predisposition , or underexcretion of urate , the salts of uric acid . Underexcretion of uric acid by the kidney is the primary cause of hyperuricemia in about 90 % of cases , while overproduction is the cause in less than 10 % . About 10 % of people with hyperuricemia develop gout at some point in their lifetimes . The risk , however , varies depending on the degree of hyperuricemia . When levels are between 415 and 530 ?mol / l (7 and 8 @@ 9 mg / dl) , the risk is 0 @@ 5 % per year , while in those with a level greater than 535 ?mol / l (9 mg / dL) , the risk is 4 @@ 5 % per year .

= = = Lifestyle = = =

Dietary causes account for about 12 % of gout , and include a strong association with the consumption of alcohol , fructose @@ sweetened drinks , meat and seafood . Other triggers include physical trauma and surgery .

Studies in the early 2000s found that other dietary factors are not relevant . Specifically , moderate consumption of purine @@ rich vegetables (e.g. beans , peas , lentils and spinach) are not associated with gout . Neither is total consumption of protein . Alcohol consumption is strongly

associated with an increased risk , with wine presenting somewhat less of a risk than beer and spirits .

The consumption of coffee , vitamin C and dairy products , as well as physical fitness , appear to decrease the risk . This is believed to be partly due to their effect in reducing insulin resistance .

= = = Genetics = = =

Gout is partly genetic , contributing to about 60 % of variability in uric acid level . The SLC2A9 , SLC22A12 and ABCG2 genes have been found to be commonly associated with gout and variations in them can approximately double the risk . Loss @-@ of @-@ function mutations in SLC2A9 and SLC22A12 cause hereditary hypouricaemia by reducing urate absorption and unopposed urate secretion . The rare genetic disorders familial juvenile hyperuricemic nephropathy , medullary cystic kidney disease , phosphoribosylpyrophosphate synthetase superactivity and hypoxanthine @-@ guanine phosphoribosyltransferase deficiency as seen in Lesch @-@ Nyhan syndrome , are complicated by gout .

= = = Medical conditions = = =

Gout frequently occurs in combination with other medical problems . Metabolic syndrome , a combination of abdominal obesity , hypertension , insulin resistance and abnormal lipid levels , occurs in nearly 75 % of cases . Other conditions commonly complicated by gout include : polycythemia , lead poisoning , kidney failure , hemolytic anemia , psoriasis and solid organ transplants . A body mass index greater than or equal to 35 increases male risk of gout threefold . Chronic lead exposure and lead @-@ contaminated alcohol are risk factors for gout due to the harmful effect of lead on kidney function . Lesch @-@ Nyhan syndrome is often associated with gouty arthritis .

= = = Medication = = =

Diuretics have been associated with attacks of gout . However , a low dose of hydrochlorothiazide does not seem to increase risk . Other medicines that do increase the risk include niacin and aspirin (acetylsalicylic acid) . The immunosuppressive drugs ciclosporin and tacrolimus are associated with gout , the former more so when used in combination with hydrochlorothiazide .

= = Pathophysiology = =

Gout is a disorder of purine metabolism , and occurs when its final metabolite , uric acid , crystallizes in the form of monosodium urate , precipitating and forming deposits (tophi) in joints , on tendons and in the surrounding tissues . Microscopic tophi may be walled off by a ring of proteins , which blocks interaction of the crystals with cells and therefore avoids inflammation . Naked crystals may break out of walled @-@ off tophi due to minor physical trauma to the joint , medical or surgical stress , or rapid changes in uric acid levels . When they breach the tophi , they trigger a local immune @-@ mediated inflammatory reaction , with one of the key proteins in the inflammatory cascade being interleukin 1? . An evolutionary loss of urate oxidase (uricase) , which breaks down uric acid , in humans and higher primates has made this condition common .

The triggers for precipitation of uric acid are not well understood . While it may crystallize at normal levels , it is more likely to do so as levels increase . Other triggers believed to be important in acute episodes of arthritis include cool temperatures , rapid changes in uric acid levels , acidosis , articular hydration and extracellular matrix proteins , such as proteoglycans , collagens and chondroitin sulfate . The increased precipitation at low temperatures partly explains why the joints in the feet are most commonly affected . Rapid changes in uric acid may occur due to factors including trauma , surgery , chemotherapy , diuretics and stopping or starting allopurinol . Calcium channel blockers and losartan are associated with a lower risk of gout compared to other medications for

hypertension .

= = Diagnosis = =

Gout may be diagnosed and treated without further investigations in someone with hyperuricemia and the classic acute arthritis of the base of the great toe (known as podagra) . Synovial fluid analysis should be done , however , if the diagnosis is in doubt . X @-@ rays , while useful for identifying chronic gout , have little utility in acute attacks .

= = = Synovial fluid = = =

A definitive diagnosis of gout is based upon the identification of monosodium urate crystals in synovial fluid or a tophus . All synovial fluid samples obtained from undiagnosed inflamed joints by arthrocentesis should be examined for these crystals . Under polarized light microscopy , they have a needle @-@ like morphology and strong negative birefringence . This test is difficult to perform and requires a trained observer . The fluid must be examined relatively soon after aspiration , as temperature and pH affect solubility .

= = = Blood tests = = =

Hyperuricemia is a classic feature of gout , but it occurs nearly half of the time without hyperuricemia and most people with raised uric acid levels never develop gout . Thus , the diagnostic utility of measuring uric acid level is limited . Hyperuricemia is defined as a plasma urate level greater than $420 \mu\text{mol} / \text{l}$ ($7 @. @ 0 \text{ mg} / \text{dl}$) in males and $360 \mu\text{mol} / \text{l}$ ($6 @. @ 0 \text{ mg} / \text{dl}$) in females . Other blood tests commonly performed are white blood cell count , electrolytes , kidney function and erythrocyte sedimentation rate (ESR) . However , both the white blood cells and ESR may be elevated due to gout in the absence of infection . A white blood cell count as high as $40 @. @ 0 \times 10^9 / \text{l}$ ($40 @, @ 000 / \text{mm}^3$) has been documented .

= = = Differential diagnosis = = =

The most important differential diagnosis in gout is septic arthritis . This should be considered in those with signs of infection or those who do not improve with treatment . To help with diagnosis , a synovial fluid Gram stain and culture may be performed . Other conditions that look similar include pseudogout and rheumatoid arthritis . Gouty tophi , in particular when not located in a joint , can be mistaken for basal cell carcinoma or other neoplasms .

= = Prevention = =

Both lifestyle changes and medications can decrease uric acid levels . Dietary and lifestyle choices that are effective include reducing intake of food such as meat and seafood , consuming adequate vitamin C , limiting alcohol and fructose consumption and avoiding obesity . A low @-@ calorie diet in obese men decreased uric acid levels by $100 \mu\text{mol} / \text{l}$ ($1 @. @ 7 \text{ mg} / \text{dl}$) . Vitamin C intake of $1 @, @ 500 \text{ mg}$ per day decreases the risk of gout by 45 % . Coffee , but not tea , consumption is associated with a lower risk of gout . Gout may be secondary to sleep apnea via the release of purines from oxygen @-@ starved cells . Treatment of apnea can lessen the occurrence of attacks .

= = Treatment = =

The initial aim of treatment is to settle the symptoms of an acute attack . Repeated attacks can be prevented by medications that reduce serum uric acid levels . Tentative evidence supports the application of ice for 20 to 30 minutes several times a day to decrease pain . Options for acute

treatment include nonsteroidal anti-inflammatory drugs (NSAIDs) , colchicine and steroids , while options for prevention include allopurinol , febuxostat and probenecid . Lowering uric acid levels can cure the disease . Treatment of associated health problems is also important . Lifestyle interventions have been poorly studied . It is unclear whether dietary supplements have an effect in people with gout .

=== NSAIDs ===

NSAIDs are the usual first-line treatment for gout . No specific agent is significantly more or less effective than any other . Improvement may be seen within four hours and treatment is recommended for one to two weeks . They are not recommended , however , in those with certain other health problems , such as gastrointestinal bleeding , kidney failure , or heart failure . While indometacin has historically been the most commonly used NSAID , an alternative , such as ibuprofen , may be preferred due to its better side effect profile in the absence of superior effectiveness . For those at risk of gastric side effects from NSAIDs , an additional proton pump inhibitor may be given . There is some evidence that COX-2 inhibitors may work as well as nonselective NSAIDs for acute gout attack with fewer side effects .

=== Colchicine ===

Colchicine is an alternative for those unable to tolerate NSAIDs . At high doses , side effects (primarily gastrointestinal upset) limit its usage . At lower doses , which are still effective , it is well tolerated . Colchicine may interact with other commonly prescribed drugs , such as atorvastatin and erythromycin , among others .

=== Steroids ===

Glucocorticoids have been found to be as effective as NSAIDs and may be used if contraindications exist for NSAIDs . They also lead to improvement when injected into the joint . A joint infection must be excluded , however , as steroids worsen this condition .

=== Pegloticase ===

Pegloticase was approved in the USA to treat gout in 2010 . It is an option for the 3 % of people who are intolerant to other medications . Pegloticase is administered as an intravenous infusion every two weeks , and reduces uric acid levels . It is likely useful for tophi but has a high rate of side effects .

=== Prophylaxis ===

A number of medications are useful for preventing further episodes of gout , including xanthine oxidase inhibitors (including allopurinol and febuxostat) and uricosurics (including probenecid and sulfinpyrazone) . They are not usually started until one to two weeks after an acute flare has resolved , due to theoretical concerns of worsening the attack . They are often used in combination with either an NSAID or colchicine for the first three to six months . They are not recommended until a person has had two attacks of gout , unless destructive joint changes , tophi , or urate nephropathy exist , because the medications have not been found to be cost-effective . Urate-lowering measures should be increased until serum uric acid levels are below $300 \pm 360 \mu\text{mol/l}$ ($5 \pm 6 \text{ mg/dl}$) and continue indefinitely . If these medications are in chronic use at the time of an attack , discontinuation is recommended . Levels that cannot be brought below $6 \pm 0 \text{ mg/dl}$ while attacks continue indicates treatment failure or refractory gout . Overall , probenecid appears to be less effective than allopurinol .

Uricosuric medications are typically preferred if undersecretion of uric acid , as indicated by a 24

@-@ hour collection of urine results in a uric acid amount of less than 800 mg , is found . They are , however , not recommended if a person has a history of kidney stones . A 24 @-@ hour urine excretion of more than 800 mg , which indicates overproduction , is an indication for a xanthine oxidase inhibitor .

Xanthine oxidase inhibitors block uric acid production . Long @-@ term therapy is safe and well tolerated and can be used in people with decreased kidney function or urate stones , although allopurinol has caused hypersensitivity in a small number of individuals . In such cases febuxostat is recommended .

= = Prognosis = =

Without treatment , an acute attack of gout usually resolves in five to seven days ; however , 60 % of people have a second attack within one year . Those with gout are at increased risk of hypertension , diabetes mellitus , metabolic syndrome and kidney and cardiovascular disease and thus are at increased risk of death . This may be partly due to its association with insulin resistance and obesity , but some of the increased risk appears to be independent .

Without treatment , episodes of acute gout may develop into chronic gout with destruction of joint surfaces , joint deformity and painless tophi . These tophi occur in 30 % of those who are untreated for five years , often in the helix of the ear , over the olecranon processes , or on the Achilles tendons . With aggressive treatment , they may dissolve . Kidney stones also frequently complicate gout , affecting between 10 and 40 % of people and occur due to low urine pH promoting the precipitation of uric acid . Other forms of chronic kidney dysfunction may occur .

= = Epidemiology = =

Gout affects around 1 ? 2 % of the Western population at some point in their lifetimes and is becoming more common . Some 5 @.@ 8 million people were affected in 2013 . Rates of gout approximately doubled between 1990 and 2010 . This rise is believed to be due to increasing life expectancy , changes in diet and an increase in diseases associated with gout , such as metabolic syndrome and high blood pressure . Factors that influence rates of gout , include age , race and the season of the year . In men over 30 and women over 50 , rates are 2 % .

In the United States , gout is twice as likely in males of African descent than those of European descent . Rates are high among Pacific Islanders and the M?ori , but rare in aboriginal Australians , despite a higher mean uric acid serum concentration in the latter group . It has become common in China , Polynesia and urban sub @-@ Saharan Africa . Some studies found that attacks of gout occur more frequently in the spring . This has been attributed to seasonal changes in diet , alcohol consumption , physical activity and temperature .

= = History = =

The term " gout " was initially used by Randolphus of Bocking , around 1200 AD . It is derived from the Latin word gutta , meaning " a drop " (of liquid) . According to the Oxford English Dictionary , this is derived from humorism and " the notion of the ' dropping ' of a morbid material from the blood in and around the joints " .

Gout has been known since antiquity . Historically , it was referred to as " the king of diseases and the disease of kings " or " rich man 's disease " . The first documentation of the disease is from Egypt in 2 @,@ 600 BC in a description of arthritis of the big toe . Greek physician Hippocrates around 400 BC commented on it in his Aphorisms , noting its absence in eunuchs and premenopausal women . Aulus Cornelius Celsus (30 AD) described the linkage with alcohol , later onset in women and associated kidney problems :

Again thick urine , the sediment from which is white , indicates that pain and disease are to be apprehended in the region of joints or viscera ... Joint troubles in the hands and feet are very frequent and persistent , such as occur in cases of podagra and cheiragra . These seldom attack

eunuchs or boys before coition with a woman , or women except those in whom the menses have become suppressed ... some have obtained lifelong security by refraining from wine , mead and venery .

In 1683 , Thomas Sydenham , an English physician , described its occurrence in the early hours of the morning and its predilection for older males :

Gouty patients are , generally , either old men , or men who have so worn themselves out in youth as to have brought on a premature old age ? of such dissolute habits none being more common than the premature and excessive indulgence in venery and the like exhausting passions . The victim goes to bed and sleeps in good health . About two o 'clock in the morning he is awakened by a severe pain in the great toe ; more rarely in the heel , ankle or instep . The pain is like that of a dislocation and yet parts feel as if cold water were poured over them . Then follows chills and shivers and a little fever ... The night is passed in torture , sleeplessness , turning the part affected and perpetual change of posture ; the tossing about of body being as incessant as the pain of the tortured joint and being worse as the fit comes on .

The Dutch scientist Antonie van Leeuwenhoek first described the microscopic appearance of urate crystals in 1679 . In 1848 , English physician Alfred Baring Garrod identified excess uric acid in the blood as the cause of gout .

= = Other animals = =

Gout is rare in most other animals due to their ability to produce uricase , which breaks down uric acid . Humans and other great apes do not have this ability , thus gout is common . Other animals with uricase include fish , amphibians and most non primate mammals . The Tyrannosaurus rex specimen known as " Sue " , however , is believed to have suffered from gout .

= = Research = =

A number of new medications are under study for treating gout , including anakinra , canakinumab and rilonacept . Canakinumab may result in better outcomes than a low dose of a steroid but costs five thousand times more . A recombinant uricase enzyme (rasburicase) is available ; its use , however , is limited , as it triggers an autoimmune response . Less antigenic versions are in development .