ejpmr, 2017,4(6), 202-211

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ReviewArticle

ISSN 2394-3211

EJPMR

THE CLINICAL FEATURES AND TREATMENT METHODOLOGIES OF GOUT

Sikander Ali, Manahil Ghazi, Syeda Manam Rubab Zahra

Institute of Industrial Biotechnology Government College University, Lahore, Pakistan.

***Corresponding Author: Sikander Ali**

Institute of Industrial Biotechnology Government College University, Lahore, Pakistan.

Article Received on 12/04/2017 **Article Revised on 03/05/2017** **Article Accepted on 24/05/2017**

ABSTRACT

Gout is the most prevalent inflammatory arthritis and affects 2.5% of the general population in the UK. It is characterized by recurrent attacks of 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. It is the only arthritis that has the potential to be cured with safe, inexpensive and well tolerated urate-lowering treatments, which reduce serum uric acid by either inhibiting xanthine oxidase – e.g. allopurinol or by increasing the renal excretion of uric acid. Of these, xanthine oxidase inhibitors are used first line and are effective in curing gout in the majority of patients. Gout can be diagnosed on clinical grounds in those with typical podagra. However, in those with involvement of other joints, joint aspiration is recommended to demonstrate monosodium urate crystals and exclude other causes of acute arthritis, such as septic arthritis. However, a clinical diagnosis of gout can be made if joint aspiration is not feasible. 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.

KEYWORDS: Tophi, Urate nephropathy, Xanthine oxidase, Allopurinol, Septic arthritis, MRI, CT, DECT.

INTRODUCTION

Gout is a form of arthritis, affecting the bones and joints. It is a metabolic syndrome and itself related to a set of disorders. The main cause of gout is known to be the accumulation of uric acid due to its improper breakdown. Hence the condition is also characterized as hyperuricemia. Gout can affect any one. Men are most likely to be affected by gout. Gout can also affect women especially after menopause. This excess of uric acid causes attacks of sudden pain in the joints. It is very painful and the affected area might get permanently disabled afterwards. Accompanied by hyperuricemia, the gout develops as the uric acid soluble concentration in the body fluids exceeds i.e., almost as higher as 400ug per liter of the blood. This high concentration of uric acid begins to form crystals which further aggravate the condition. Sometimes this deposition of crystals is silent and painless which is referred to as gouty tophus.[1]

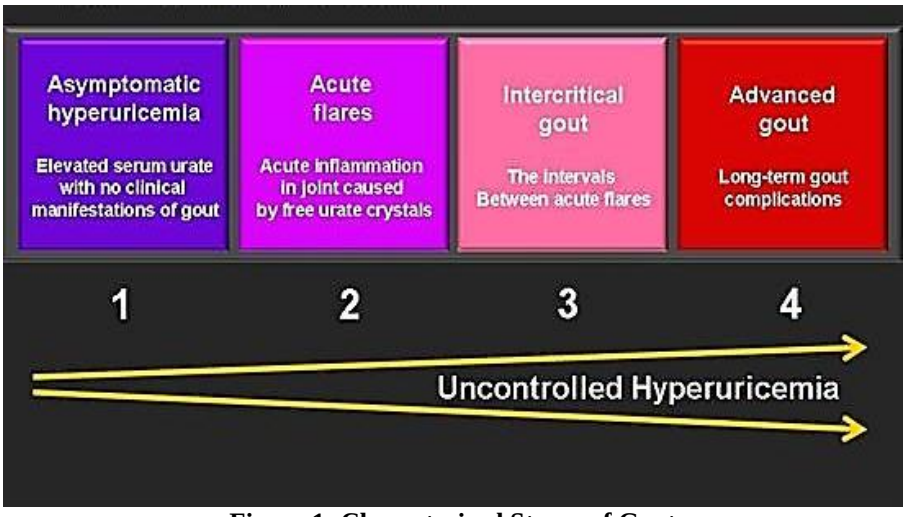

Figure 1: Characterized Stages of Gout

It was Garrod who almost 150 years ago identified that uric acid is elevated in the blood of gout patients, a condition that can be referred as hyperuricemia. This deposition of uric acid can occur in other tissues as well, not necessarily the joints. Hence it is also a leading cause for tophi, nephropathy, and kidney stones. The condition has its various stages of attack; however, the separation between the stages may be incomplete. In some cases, stage 1 can reflect the complete disease. Uric acid concentration of blood serum may continue to rise but is symptomless and would be referred to as its first developing stage. Then the second stage, acute gouty arthritis develops. Almost 40 to 60 percent of the acute gout may develop chronic gout within a year and its conditions worsen. However, if left untreated, further complications are observed.[2] Figure 1 shows some of the characterized stages of gout.

SYMPTOMS

Excess of uric acid causes attacks of sudden pain in the joints. The joints are more likely to be swelled, redden and become stiff making it difficult to move the affected joint. The big toe is most likely to be affected by the gout i.e., the joint at the base of the toe. The attacks of pain can occur several times in a particular period until the disorder is treated completely. Prolonged gout continues to affect the joints, tendons that attach these joints to muscles and also nearby tissues. The pain originates mostly in the midnight and seems to be unbearable when given any stress or weight on it. The attack of such pain can prolong from a few days until many weeks. However, the next attack may not occur for even several months or years. Even though no painful sensation is felt, the buildup of urate crystals keeps on damaging the joints.[3] The joint may deform in shape (Fig. 2).

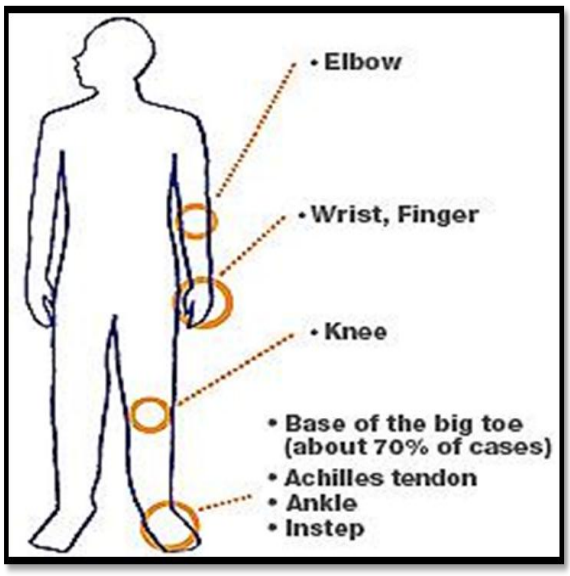

Figure 2: Vulnerable joints to be affected by Gout

The most commonly observed signs and symptoms of gout occurring mostly at night include intense joint pain in the big toe usually, but can also occur feet, ankles, knees, hands and wrists which is very much intense in the first 4 to 12 hours. Lingering discomfort which is the after-pain, occurring after the major pain subsides. Sometimes the joint pain continues for days or weeks. These later attacks prolong for even larger durations and thus affecting more joints. Other symptoms include inflammation and redness in the affected joint which definitely become swollen red and is also hotter than the nearby tissues or cells. Also there remains only a limited range of motion in the affected part. As the gout progresses, the effected joints lessen in their ability of making appropriate movements.[4]

CAUSES

Excess of uric acid can cause gout. Excess of uric acid is not always harmful, many of the people having higher level of uric acid does not develop gout, but when level of uric acid gets high in blood they form crystals in joints which cause inflammation and severe kind of pain. Normally much of the uric acid is excreted through urine. Uric acid dissolves in the blood, carried to kidney and then removed but urate crystals form when this normal path way is disturbed. This happens when either the body began to produce too much uric acid or the kidneys fail to excrete this excessive uric acid. The result is the formation of its crystals (urate crystals) which deposit into the joints.[5]

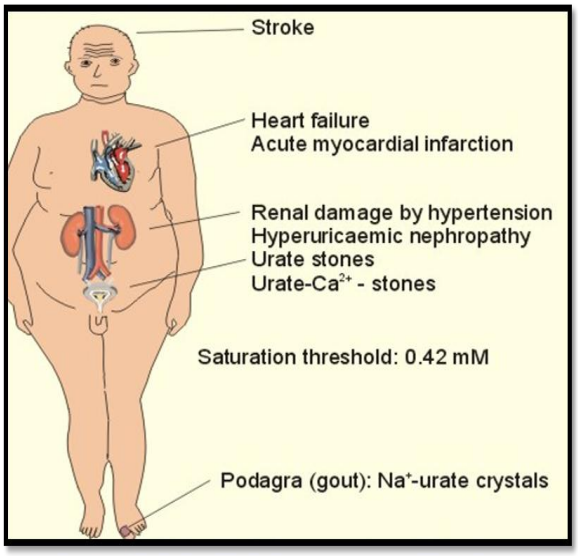

Figure3. Further complications in the Gout condition

Chances of gout are higher on people who are overweight. The chances increase more if the meal of such people includes fish or meat, sea food and steaks. This is because of the fact that fish and meat contains chemicals that ultimately forms purines in the body after their intake. Actually purines after their breakdown lead to the formation of uric acid. However, a moderate consumption of purine containing diet doesn't cause gout. Also the risk is higher in people who drink too much alcohol, beer, wine and fructose containing drinks. After alcohol consumption, there is a great breakdown of ATP and lactic acid which increases the uric acid load

and minimizes its elimination from the body. Fructose is the only sugar that increases the uric acid load because it also enhances the ATP breakdown like alcohol. Not only this, it develops insulin resistance thus reducing the amount of uric acid excretion by kidneys. Medicines like diuretics can cause gout too. Hypertension can also cause gout. A patient of gout has more chances of getting a heart attack or heart failure.[6] Figure 3 explain the complications caused by gout.

Risk factors

The causative factors for gout are quite numerous. Diet is one of them. The chances increase more if the meal of such people includes fish or meat, sea food, steaks. This is because of the fact that fish and meat contains chemicals that ultimately forms purines in the body after their intake. Actually purines after their breakdown lead to the formation of uric acid.[7]Also the risk is higher in people who drink too much alcohol, beer, and fructose containing drinks. Chances of gout is higher on people who are over-weight because if one is obese the body produces much uric acid which in turn is difficult for the kidney to eliminate and chances of getting gout are greater[8]. Figure 4 shows relative incidents of gout caused by alcohol intake.

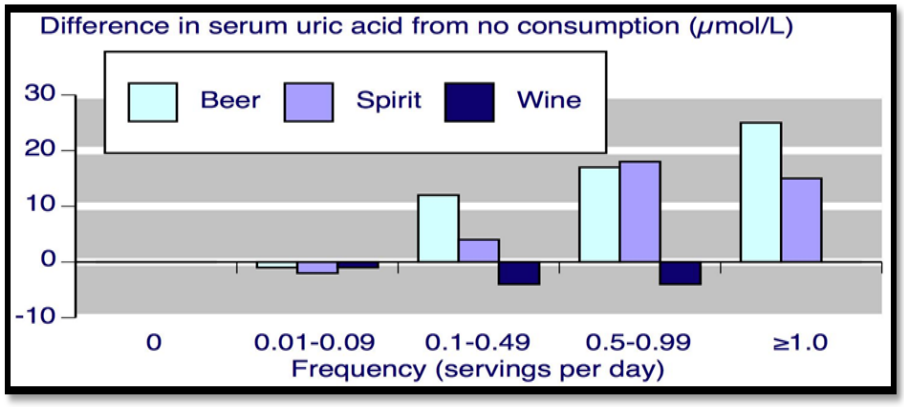

Fig 4: Relative incidents of gout caused by alcoholic beverages

Some conditions and diseases enhance the risk for gout. These include untreated high blood pressure, diabetes, metabolic syndrome, heart diseases, and kidney diseases. Family history of gout can also be an important risk factor. If the ancestors of the family have had gout the chances of having gout are greater in the progeny.[8] Another factor includes the age and sex of an individual. Chances of having gout are more in men as compared to women due to menstruation but after menopause the level become same as men. Gout is common in men in age of 30-50 year whereas women develop the symptoms after menopause. The factors of minor importance include recent surgical operation such as surgery or trauma is also linked with greater risk of having gout.[9][10] Also the socioeconomic conditions of a country also determine the particular risk of developing gout for that country.[11] Table 1shows risk factors and frequency of gout.

Table 1: Risk factors of Gout and their relative risks

RISK FACTOR	NOTES	RELATIVE RISK
Diuretic use	—	3.37 (2.75 to 4.12)
Alcohol intake	≥ 50 g per day vs. none	2.53 (1.73 to 3.70)
Beer	≥ 2 drinks per day vs. none	2.51 (1.77 to 3.55)
Spirits	≥ 2 drinks per day vs. none	1.60 (1.19 to 2.16)
Wine	≥ 2 drinks per day vs. none	1.05 (0.64 to 1.72)
Hypertension	—	2.31 (1.96 to 2.72)

EPIDEMIOLOGY

There has ban a significant difference between the epidemiology of gout within different countries because of the differences in their methodologies, lifestyle and diet etc. This distribution of gout is very uneven across the countries. The risk is affected by seasons, age, and sex and also by the race of the individual. The seasons also can determine the risk of developing gout; some studies state that in spring season, the risk is higher. This can be because of the changes in the diet, temperature and physical wok activity of the individuals which is affected by the particular season.[12] Globally, the gout burden has increased a lot over the past 50 years. Gout is prevalent more in males than females. Males over the age of 30 are most vulnerable however, for females age is extended up to 50 years after which they become more vulnerable to gout after menopause because of the decreased effect of hormones like oestrogen, progesterone etc.[13] The rate of being affected by gout in both the males above 30 years and females above 50 years is approximately 2 percent (Fig 5).

Table 2: Incidence and Prevalence of Gout in Respective years

SOURCE	YEAR	PREVALENCE	INCIDENCE
National health and nutrition survey (NHANES III)	1988 to 1994	5.1 million	NR
US manage care claims Database	1990 1999	2.9 to 5.2 /100,000 persons	NR
Rochester Epidemiology Project	1977 to 1976 1995 to 1996	NR	45 to 62.3/ 100,000 persons
National health interview survey	1992 1996	2 million	>46% in men >2% in women

Gout is very much prevalent in the people of Pacific region which include Canada, china, japan, Australia, chile, combodia, Singapore, South Korea and others. Australian men have high serum uric acid concentration. Sub-Sahara Africa and Polynesia are also affected adversely.[14] However, surprisingly, developed countries have more incidence and risk of gout disorder as compared to the developing countries.[14] In the west, about 1 to 2 per cent of the population gets affected by gout. The disease is becoming more common there day by day. In 2013, at least 5.8 million people were gout patients around all the western countries. Overall rate of gout in western countries increased to double during 1990 to 2010 due to increasing high blood pressure in the population, changes in the diet, efforts to increase life expectancy etc. The African migrants of America have twice the risk of gout than the European migrants.[15] (Table 2).

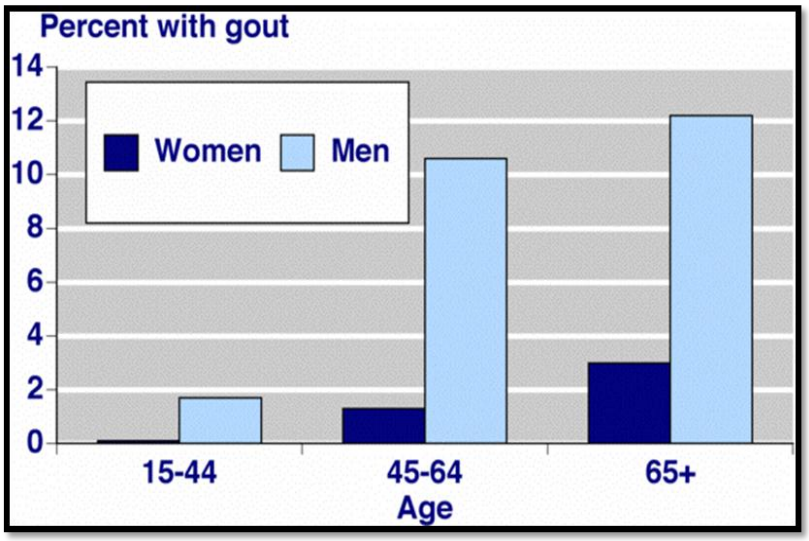

Figure 5: Comparative increasing risk of gout with age in men and woman

PATHOGENESIS AND PATHOPHYSIOLOGY

Gout is actually because of the improper metabolism of purine, whose breakdown product uric acid begins to accumulate as the crystals. Uric acid picks up the sodium ions and form monosodium urate crystals in joints or tendons and in the nearby tissues. If the crystals are small, a set of proteins totally surround it and avoid its contact with the nearby cells, thus no inflammation is produced.[16] Continuous an 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 damage to the joint, medical or surgical stress, or rapid changes in uric acid levels. When they break through the tophi, they trigger a local immune-mediated inflammatory reaction in macrophages, which is initiated by the NLRP3 in flammasome protein complex. Activation of the NLRP3 in flammasome recruits the enzyme caspase 1, which converts pro-interleukin 1β into active interleukin 1β, one of the key proteins in the inflammatory cascade.[17] (Fig 6).

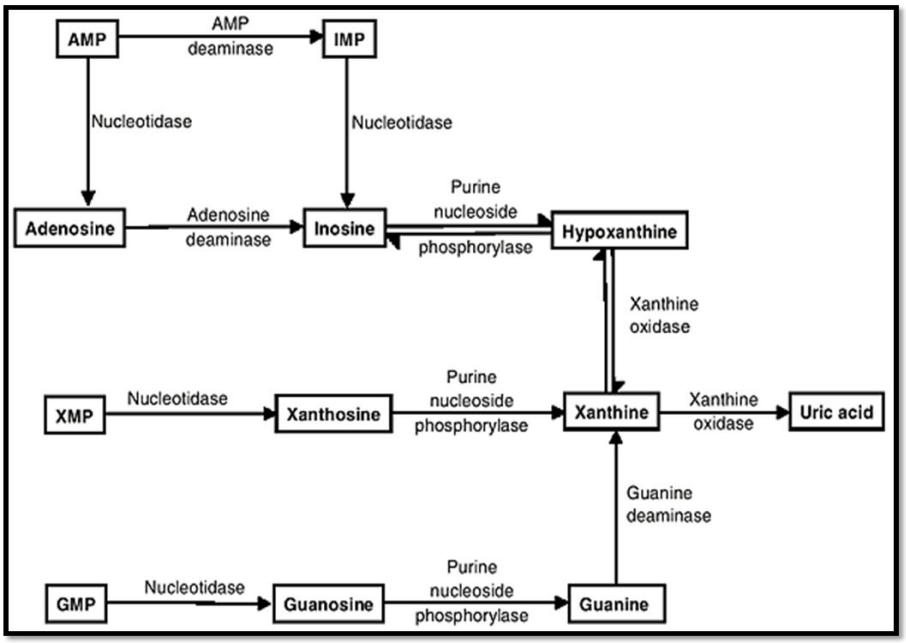

Figure 6: Pathways responsible For Uric acid production in body

Out of the two main factors which include over production by the body and under excretion by the kidneys, the under excretion comprises of 70 percent of the uric acid load. Various transporters of uric acid have been known in the kidney tubules and intestinal tract showing the pathway and accumulation of excessive uric acid- hence showing the pathogenesis pathway of gout. The uric acid might exist in the form of monosodium urate crystals in the kidneys. Increase of monosodium urate crystals increases the risk of gout. However, all hyperuricemic patients might not develop gout at all. Normally the 30 percent of the purines come from the diet and the rest 70 percent is synthesized by the body itself through the nucleotides synthesis and metabolism etc. The fate of purines is its breakdown to uric acid ultimately.[18]

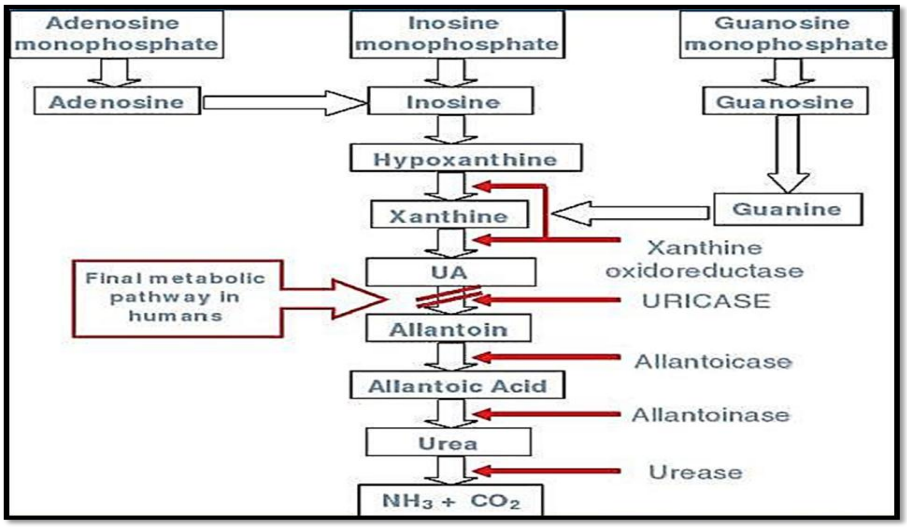

Figure 7: Defective uric acid metabolism in gout patients (the uricase enzyme doesn't act on uric acid and it begins to accumulate as crystals in the joints etc.)

Under normal conditions the uric acid is excreted directly through kidneys and through the gut or either it breaks down allatoin and then to urea and then to ammonia finally. However, in gout the enzyme uricase is defective or non- functional or partly functional hence the uric acid began to accumulate in the body in the form of crystals and deposits in joints and tissues etc. The monosodium crystals deposits of the uric acid induce the inflammation response by activating certain components of immune system. The macrophages try to phagocytosis the crystals by activating NALP-3 inflammasome, which in turn directs inflammation. The white blood cells proliferates and antibodies are released which generates an intense response of pain. White blood cells release phagocytizing lysozymes for these monosodium crystals. Complement protein pathways and toll like receptors are

also activated to perform their work against the crystals.[19] (Fig 7).

TYPES OF GOUT ON THE BASIS OF DIFFERENT FEATURES

Acute gout

Acute gout attacks are characterized by typical features of acute crystal synovitis, such as rapid onset (symptoms peaking within 12–24 hours of onset), excruciating joint pain, exquisite tenderness to touch, erythema and articular/periarticular swelling. The attack usually resolves in 1–2 weeks.[20]In acute gout, there is an inflammation of synovial membrane with severe joint pain, sensitive to touch, erythema and joint swelling. Metatarsophalangeal joint is most affected. In addition ankle, mid foot, wrist, knees and elbows can also be affected. Onset of acute gout occurs in lower limb and then poly-articular regions are affected. It may be caused by an injury, excess alcohol intake or may be due to dehydration.[21] (Fig.8 i).

Chronic tophaceous gout

It involves chronic joint pain, increase in sensitivity and stiffness of joints with attacks of acute gout. It occurs after many year attacks of acute gout. It involves formation of nodules having MSU crystals which appears as white colour to yellow firm subcutaneous masses usually in feet and finger tips, also found in the olecranon and pre-patellar bursae.[22][23] (Fig 8 ii)

Transplant-associated gout

It can develop within three to five years in transplant recipients. It occurs in patients having immunosuppressed solid organ transplant and receive very low dose of steroid prednisolone as well as low dose of calcineurin inhibitors e.g. cyclosporine.[23]

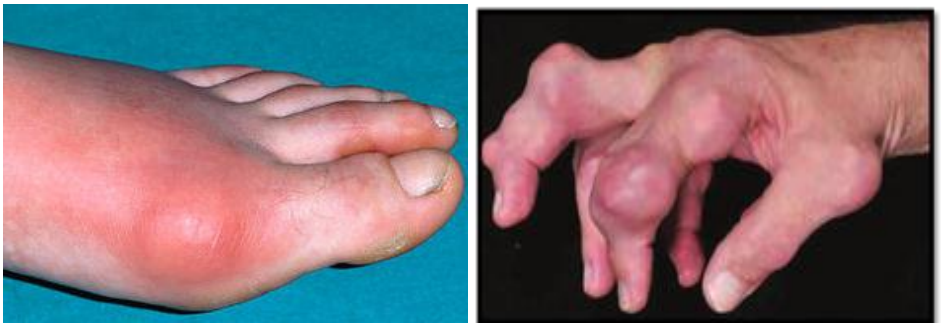

Figure 8: i. acute gout ii. Chronic gout

Comorbidities

The patients of gout have several other disorders like hypertension, obesity, ischemic heart disease and congestive cardiac failure as well as insulin resistance, hyperlipidemia and renal impairment are very common. The presence of these diseases must be properly treated.[23] (Table 3).

Table 3: Comorbidities associated with Gout

COMORBIDITIES	
Over weight / Obesity	>71
Insulin resistance syndrome	63%
Type II diabetes	15%
Renal insufficiency	5%
Kidney stones	14-15 %

INVESTIGATION AND DIAGNOSIS

USING BODY FLUIDS: Gout is diagnosed by polarized light microscopy of peripheral blood, synovial fluid and by urinary uric acid excretion.[24]

Peripheral blood

Peripheral blood can be used for the diagnosis of gout. In case of acute gout, the concentration of neutrophils and other inflammatory markers is very high. So by seeing its concentration, acute gout can be diagnosed. Similarly the concentration of SUA is reduced in acute gout. So, it can be checked after two to three weeks of the attack and can be diagnosed. The most common method is to check hyperuricemia. For the chronic kidney disease myeloproliferative disorders, it is necessary that they should be diagnosed by seeing liver function, glucose level, lipid profile, proper renal function as well as the full blood count.[25]

Synovial fluid

By using synovial fluid of affected joint and by the proper examination of the aspirated synovial fluid through plain light microscopy as well as with the help of polarized light microscopy, it is found that this fluid is turbid having low viscosity. For the diagnosis of septic arthritis we can also perform Gram stain procedure as well as culturing aspirated synovial fluid. We can also perform leukocyte counts of the synovial fluid which may be >10,000/mm.[26]

Urinary uric acid excretion

xanthine oxidase inhibitors (XOIs) are dangerous in treating gout and should be checked in patients having premature onset of gout i.e. before the age of 25 years. So, this method of diagnosing gout is rarely performed. 24-hour urine collection is usually done for analyzing uric acid creatinine ratio.[27][28]

CLINICAL METHOD AND IMAGING

Radiography

This method of diagnosing gout is helpful in later stages of gout. The latest study is carried out for radiographic damage index of chronic gout. It is such an amazing scoring system which that is necessary for determination of the impact of lowering of urates on radiographic damage. This method also helps in guiding the therapy of patients having chronic gout. This method of diagnosis is very feasible and reproducible.[29] These damage indexes also associate with the functional capacity. A comparison of radiography with computed tomography is used for the assessment of gouty erosions.it is found that assessment of joints for erosion by using plain radiography technique is less reliable because of its small size and due to some degenerative joint disease.[30] (Fig 9).

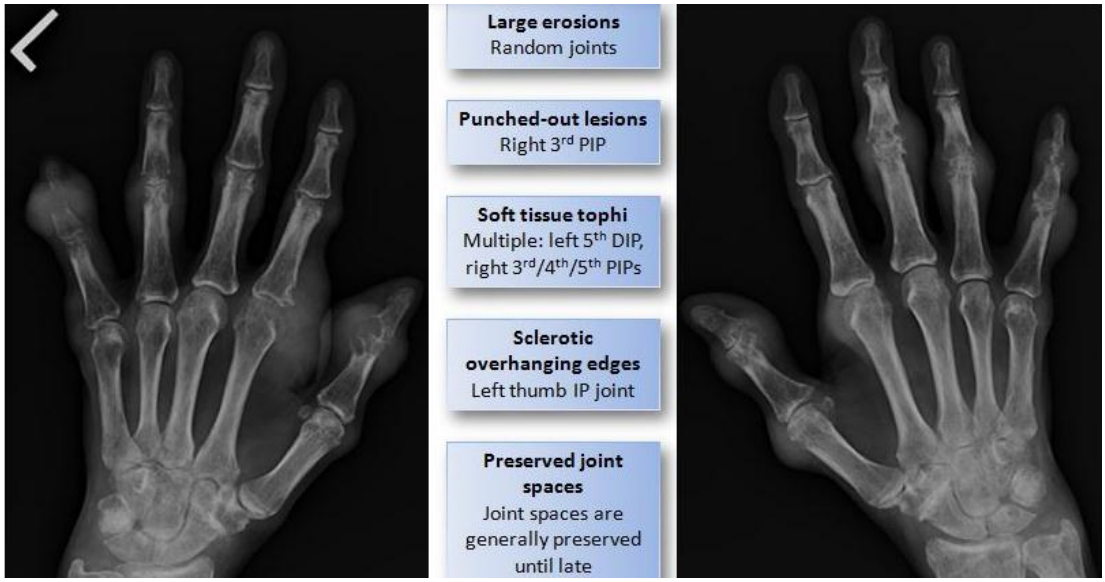

Figure 9: Radiographic findings in Gout

Ultrasound

Ultrasound has very high resolution which helps us to diagnose gout and find out early diagnosis, taking a therapeutic decision and treating the gout. This method also helps to assess the extent of lesions and its therapeutic response. By comparing sonography with X-ray, we find ultrasonography is more sensitive, non-invasive, can differentiate between cystic and solid lesions.[31][32]It also helps in guidance of biopsies as well as punctures it is relatively low cost method of diagnosis. It is useful as it does not use ionizing radiations. It can detect early changes that take place in soft tissues. This method is easy to repeat and can be used of dynamic assessment of the tendons as well as joints. [33][34] (Fig 10).

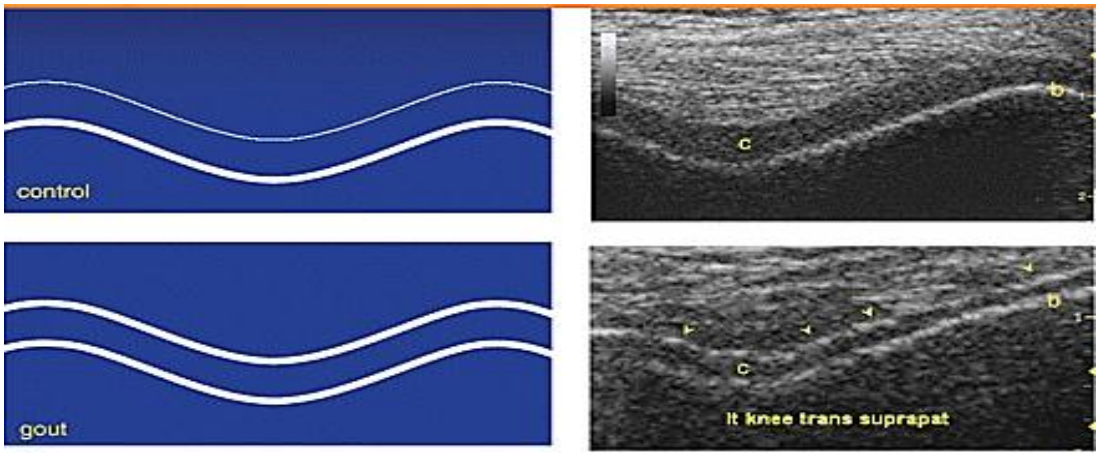

Figure 10: Ultrasound analysis of gout affected bone compared to the normal bone as control

Computed Tomography (CT)

This technique is more sensitive than X-ray and MRI. It is basically used for identification of bone erosion. The presence of tophi in intra-articular areas as well as in the subcutaneous tissues can be diagnosed by computed tomography. It helps in differentiation of different types of soft tissue nodules and used to evaluate the damage that occur in the deeper structures like spine which are usually not detected by using other methods that do not use ionizing radiation. The limitation of this method is that this method is not recommended for diagnosis of gout on surface structures as it involves ionizing radiation exposure.[35] (Fig 11).

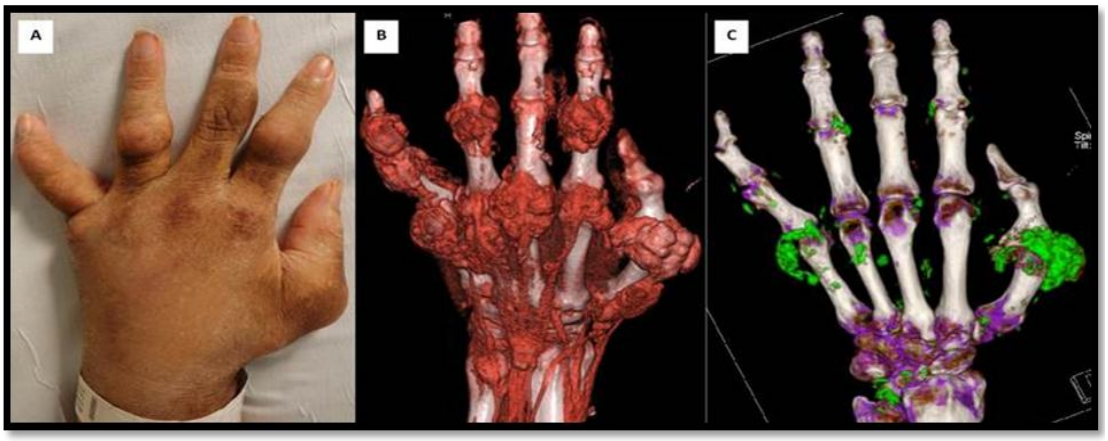

Figure 11: Computed Tomographic analysis

(A= Evident gout in fingers on clinical examination B= Computed tomography showing the 3D volume of affected region C= Dual energy computed tomography of showing severity in joints)

Dual-energy computed tomography (DECT)

Basically this method is used for differentiating MSU crystals from that of gout and bone calcification. This technique is useful to confirm gout in patients having normal level of uric acid, excluding the disease in the patients which have hyperuricemia. DECT provides knowledge of chemical composition of tissues and help in their differentiation. This technique is size limited usually of 2 mm so we are not able to detect deposits of size below this. This method is susceptible to artifacts in thickened skin areas e.g. heel as well as nails. Its diagnostic efficiency is low i.e. 50 percent. Its role is limited due to high cost and due to ionizing radiation exposure to patient.[35]

Magnetic Resonance Imaging (MRI)

This method is used for differential diagnosis of the masses of soft tissues. It can detect early stage of articular erosions which are not detected by radiography.it can be used to find out actual cause of painful disorders that changes structure of bones. It is however, not a routine diagnostic method for tophaceous gout. By this method, tophi appearance seems to be variable.it gives morphology of tophi. This method is not favorable for early gout diagnosis.[36] (Fig. 12).

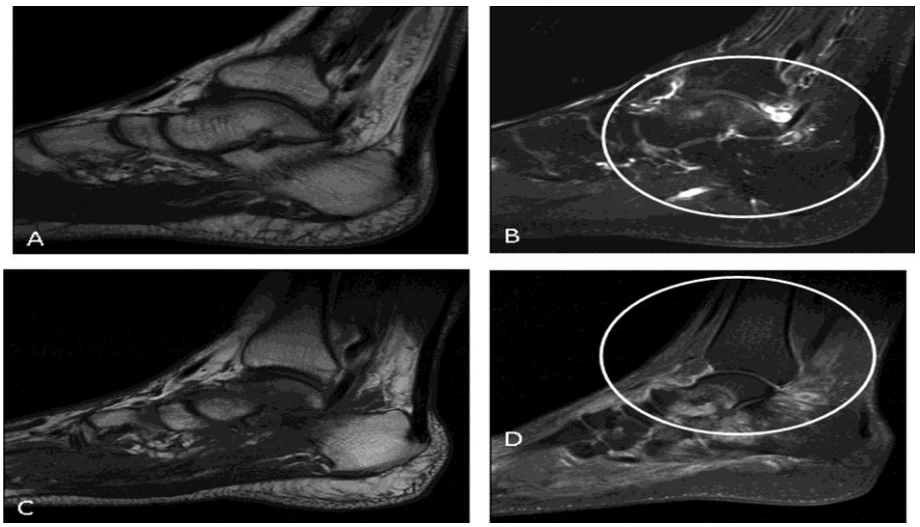

Figure 12: Magnetic resonance imaging of gout affected foot (A and C showing X ray imaging while B and D showing the affected points)

Treatments and drugs

Gout is mainly treated with drugs like colchicine which is in fact pain killer for gout. Its low dose is prescribed for acute gout. Non-steroidal anti-inflammatory drugs (NSAIDs) include ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve, others), as well as indomethacin and celecoxib (Celebrex) which are very powerful.[37] Corticosteroids are also recommended for patients that are not able to take NSAIDs. They control pain and inflammation of gout. Corticosteroids are usually injected in joints. Side effects of these drugs may include high blood pressure, elevation of blood sugar and may include change in mood**.** Xanthine oxidase inhibitors include allopurinol (Aloprim, Zyloprim) as well as febuxostat (Uloric) are some of the important drugs that inhibit and block uric acid production by the body, hence, reducing risk of gout. Another drug that lowers the level of uric acid reducing risk of gout, while increasing level of uric acid in urine is Probenecid.[38][39] (Table 4)

TABLE 4: Gout's treatment drugs, cautions associated to them and the particular effect they cause

Treatment drugs	Associated cautions	Related affects
NSAIDs		
Indomethacin 50 mg tid (4-10 days) Naproxen 500 mg bid (4-10 days) Sulindac 200 mg bid (4-10 days)	Elderly patients, renal insufficiency, heart failure, peptic ulcer, liver disease, and concurrent anticoagulants (interacts with warfarin)	All NSAIDs are effective
Corticosterols		
Prednisone 20-40 mg daily (2-3 days; taper over 10-14 days) Intra-articular methylprednisolone 20-40 mg dose	Avoid in patients with septic joints; use with caution in patients with diabetes	Intra-articular therapy is treatment of choice if 1 or 2 accessible joints are involved
Colchine		
0.6 mg orally bid 0.6 mg orally daily or q48h (depending on renal clearance)	Avoid in severe renal or hepatic impairment because it can lead to bone marrow suppression and neuromyopathy	Use within first 24 hours of the attack; reduce dosage in older patients; diarrhea limits its use

Gout treatment other than drugs include limiting use of alcohol, limit drinks having fructose, drinking plenty of water, exercising regularly, weight loss and limiting food which is rich in purines like sea food, red meat, organ meat etc.[40][41][42] Use of coffee also lower uric acid level. Taking supplements having vitamin C and eating fruits rich in it like oranges decrease blood uric acid level. Gout attacks are reduced by eating cherries and taking drinks having cherry extract. Many other techniques including relaxation methods like deep-breath exercises also provide relieve from gout.[43][44][45]

CONCLUSION

Gout is a disease caused by defect in metabolism due to hyperuricemia. It is actually because of the improper metabolism of purine, whose breakdown product uric acid begins to accumulate as the crystals It causes pain in joint, swelling and redness of bones. Acute gout, chronic tophaceous gout, transplant associated gout are its types. Risk factors include drinking alcohol too much and other genetic factors.it can be diagnosed by using body fluid like blood, synovial fluid and urine. Imaging methods include X-ray, MRI, ultrasound, radiography, computed tomography etc. It is treated by weight loss, taking food rich in vitamin C and avoiding alcohol. Medication includes NSAIDS, steroids and colchicine.

REFERENCES

1. Chen LX, Schumacher HR: Gout: an evidence based review. J Clin Rheumatol, 14(5): S55-62.
2. Rose DM, Liu-Bryan R: Innate immunity in triggering and resolution of acute gouty inflammation. Curr Rheumatol Rep., 2006; 8: 209–14.
3. Aringer M, Graessler J: Understanding deficient elimination of uric acid. Lancet, 2008; 372: 1929–30.
4. Shoji A, Yamanaka H,Kamatani N:A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy.Arthritis Rheum, 2004; 51: 321–5.
5. Chana A, Lee G, Dalbeth N. Factors influencing the crystallization of monosodium urate: a systematic literature review. BMC Musculoskelet Disord, 2001; 16: 296.
6. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. Am J Med., 2006; 119(9): 800.e13-800.
7. MacFarlane LA, Kim SC. Gout: a review of non-modifiable and modifiable risk factors. Rheum Dis Clin North Am, 2014; 40: 581 – 604.
8. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. Am J Med., 2006; 119(9):800.e13-800.
9. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet, 2004; 363: 1277–81.

10. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purinerich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med., 2004; 350: 1093–103.
11. Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. J Rheumatol, 2006; 33: 1341-5. [Erratum, J Rheumatol, 2006; 33: 1714.]
12. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis., 2015; 74: 661 – 7.
13. Weaver AL: Epidemiology of gout. Cleve Clin J Med., 2008; 75: 9–12.
14. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum, 2011; 63: 3136 – 41.
15. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R:Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 2004; 31: 1582–7.
16. Pillinger MH, Rosenthal P, Abeles AM. Hyperuricemia and gout: new insights into pathogenesis and treatment. Bull NYU Hosp Jt Dis., 2007; 65: 215–21.
17. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med., 200Z; 143: 499–516.
18. Busso N, So A. Gout. Mechanisms of inflammation in gout. Arthritis Res Ther., 2010; 12: 206.
19. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout associated uric acid crystals activate the NALP3 inflammasome. Nature, 2006; 440: 237–41.
20. Taylor WJ, Fransen J, Jansen TL et al. Study for Updated Gout Classification Criteria (SUGAR): identification of features to classify gout. Arthritis Care Res., 2016; 68: 1894–8.
21. Sutaria S, Katbamna R, Underwood M: Effectiveness of interventions for the treatment of acute and prevention of recurrent gout— a systematic review .Rheumatology (Oxford), 2006; 45: 1422–31.
22. Kydd AS, Seth R, Buchbinder R, Edwards CJ, Bombardier C. Uricosuric medications for chronic gout. Cochrane Database Syst Rev., 2014; (11): CD010457.
23. Li-Yu J,Clayburne G,Sieck M et al.: Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol, 2001; 28: 577–80.
24. Gálvez J, Sáiz E, Linares LF, Climent A, Marras C, Pina MF, et al. Delayed examination of synovial fluid by ordinary and polarised light microscopy to detect and identify crystals. Ann Rheum Dis., 2002; 61: 444-7.
25. Yuan S, Bien C, Wener MH, Simkin P, Rainey PM, Astion ML. Repeat examination of synovial fluid for crystals: is it useful? Clin Chem., 2003; 49: 1562-3.
26. Wan A, Amer H, Dieppe P. The value of synovial fluid assays in the diagnosis of joint disease: a literature survey. Ann Rheum Dis., 2002; 61: 493-8.
27. Schlesinger N, Baker DG, Schumacher HR,Jr. How well have diagnostic tests and therapies for gout been evaluated? Curr Opin Rheumatol, 1999; 11: 441–5.
28. Pascual E,Sivera F:Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. Ann Rheum Dis., 2007; 66: 1056–8.
29. Schueller-Weidekamm C, Schueller G, Aringer M, Weber M, Kainberger F: Impact of sonography in gouty arthritis: Comparison with conventional radiography, clinical examination and laboratory findings. Eur J Radiol, 2007; 62: 437–442.
30. Rousseau I, Cardinal EE, Raymond-Tremblay D, Beauregard CG, Braunstein EM, Saint-Pierre A. Gout: radiographic findings mimicking infection. Skeletal Radiol, 2001; 30: 565-9.
31. Scirocco C, Rutigliano IM, Finucci A, Iagnocco A. Musculoskeletal ultrasonography in gout. Med Ultrason, 2015; 17: 535-40.
32. Chowalloor PV, Keen HI. A systematic review of ultrasonography in gout and asymptomatic hyperuricaemia. Ann Rheum Dis., 2013;72:638-45
33. Puig JG, de Miguel E, Castillo MC, Rocha AL, Martínez MA, Torres RJ: Asymptomatic hyperuricemia: impact of ultrasonography. Nucleosides Nucleotides Nucleic Acids, 2008; 27:592–5.
34. Gutierrez M, Schmidt WA, Thiele RG, Keen HI, Kaeley GS, Naredo E, et al. International Consensus for ultrasound lesions in gout: results of Delphi process and web-reliability exercise. Rheumatology (Oxford), 2015; 54:1797-805.
35. Gentili A. The advanced imaging of gouty tophi. Curr Rheumatol Rep., 2006; 8: 231-5.
36. Poh YJ, Dalbeth N, Doyle A, McQueen FM. Magnetic resonance imaging bone edema is not a major feature of gout unless there is concomitant osteomyelitis: 10-year findings from a high-prevalence population. J Rheumatol, 2011; 38:2475-81.
37. Gast LF: Withdrawal of longterm antihyperuricemic therapy in tophaceous gout. Clin Rheumatol, 1987; 6: 70–3.
38. Lieshout-Zuidema MF, Breedveld FC: Withdrawal of longterm antihyperuricemic therapy in tophaceous gout.J Rheumatol, 1993; 20: 1383–5.
39. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol, 2004; 31: 2429-32.

40. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. J Rheumatol, 2002; 29: 331-4.
41. Reinders MK, van Roon EN, Jansen TL et al.: Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol.Ann Rheum Dis., 2009; 68: 51–6.
42. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R: Prophylactic colchicine therapy of intercritical gout. A placebocontrolled study of probenecid-treated patients. Arthritis Rheum, 1974; 17: 609–14.
43. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol, 2010; 22: 165–72.
44. Williams PT:Effects of diet,physical activity and performance and body weight on incident gout in ostensibly healthy, vigorously active men. Am J Clin Nutr, 2008; 87: 1480–7.
45. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis., 2006; 65: 1301-11.