

# A review of the pathogenesis of gouty arthritis

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**ABSTRACT:** A common and severe form of inflammatory arthritis is gout. It occurs when monosodium urate crystals accumulate in tissues. Millions of outpatient visits are due to gouty arthritis each year, and the prevalence is rising. Hyperuricemia, or high serum uric acid levels, is the biological precursor to gout. The formation of uric acid crystals requires an increase in serum uric acid above a particular threshold. Since 99 percent of the molecules at physiologic pH are in the form of urate, the term "urate" is used in this sense rather than the more popular term, "uric acid". Considering that the uric acid saturation threshold in biological fluids is 7.0 mg/dl, uric acid concentrations in a healthy person's blood are at 6.0 mg/dl. Local tissue macrophages are stimulated by monosodium urate crystals to release inflammatory cytokines, including IL1. The typical pathophysiologic characteristic of acute gout is the neutrophilic influx that is caused by these mediators along with complement. High protein intake and a variety of purine-rich meals have long been considered gout risk factors. OAT1 and OAT3 may be crucial in the etiology of hyperuricemia. Gout is a known result of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency. The primary mechanism for the reabsorption of urate in the human kidney is URAT-1, which belongs to the family of organic anion transporters. Gout and hyperuricemia are linked to URAT-1 gene mutations.

**KEYWORDS:** Gout, Hyperuricemia, HGPRT deficiency, Purine rich foods, URAT.

## I. INTRODUCTION

Monosodium urate crystals depositing in tissues cause systemic illness gout [1]. Millions of outpatient visits are due to gouty arthritis each year, and the prevalence is rising [2]. Gout is a serious global health concern that appears to be spreading worldwide over the past 50 years. The majority of cases have been linked to Oceanian nations, particularly in Maori and Taiwanese aboriginals, where some estimates put the incidence at >10%. Most of North America and Western Europe have high rates of gout, ranging from 1 to 4 percent. Gout is uncommon in areas of the former Soviet Union, Guatemala, Iran, Malaysia, the Philippines, Saudi Arabia, rural Turkey, and countries in Africa. Studies' estimates of the prevalence of gouty arthritis range due to varying age groups, sex distributions, and geographic areas [3].

Hyperuricemia, or high serum uric acid levels, is the physiologic precursor to gout [2]. The development of uric acid crystals requires an increase in serum uric acid over a particular threshold. Even though hyperuricemia is the primary pathogenic abnormality in gout, many people with it never even experience gout or the formation of uric acid crystals. In actuality, gout only occurs in 5% of individuals with hyperuricemia above 7 mg/dL. As a result, it is believed that additional factors, like genetic predisposition, contribute to the occurrence of gout [1]. Since 99 percent of the molecules at physiologic pH are in the form of urate, the term "urate" is used in this circumstance rather than the more popular term, "uric acid." The majority of molecules only take the form of uric acid in regions of the urinary tract where the pH is below 5.7; but, due to uric acid's weaker solubility, it may also be present as uric acid crystals [4].

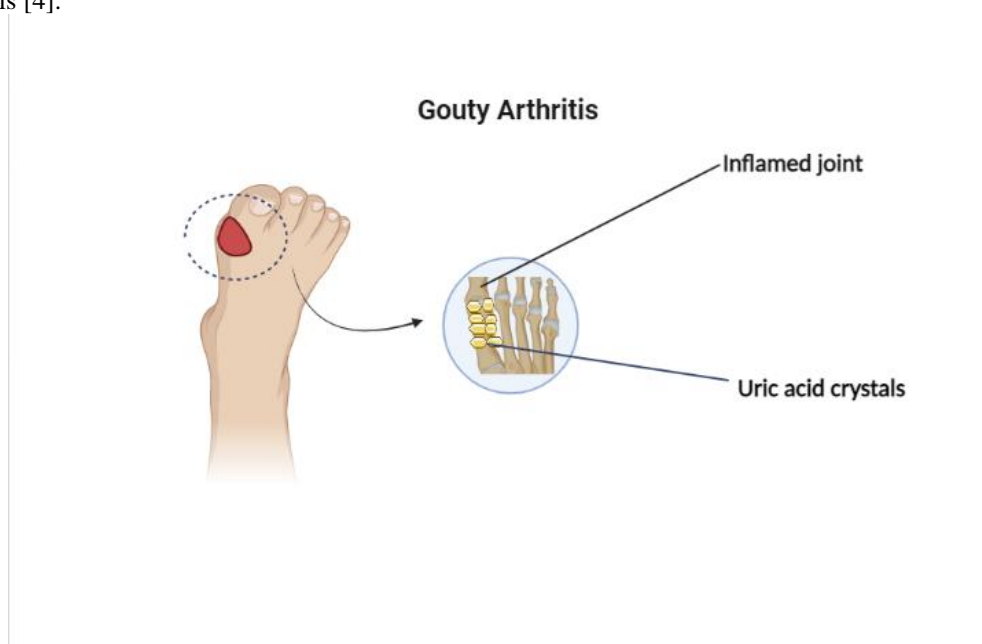


Fig 1: Gouty arthritis in the big toe

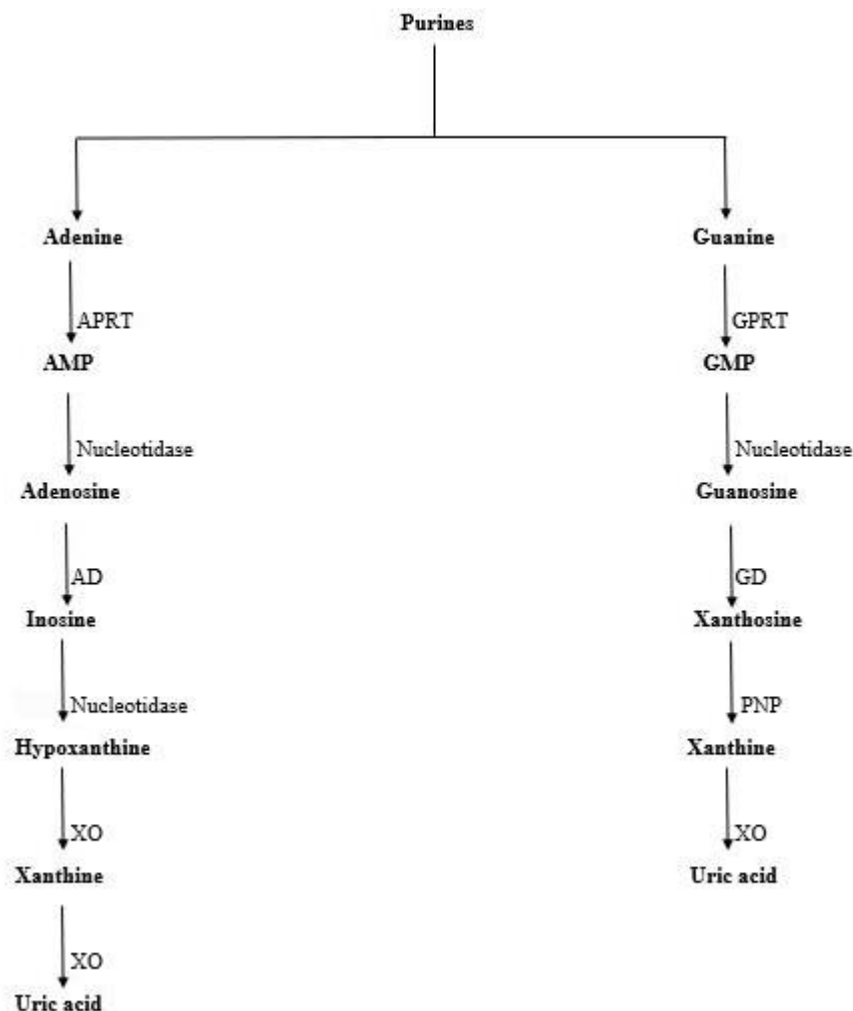
**II. PHYSIOLOGY OF URIC ACID**

As part of the regular turnover of nucleic acids, uric acid is produced. This molecule is formed when xanthine oxidase, an enzyme found in the peroxisomes of most cells, oxidizes purines, such as those found in DNA or RNA. As a result of this ongoing activity, uric acid is a regular component of intracellular fluids and biological systems. Considering that the uric acid saturation threshold in biological fluids is 7.0 mg/dl, uric acid concentrations in healthy persons' blood are at 6.0 mg/dl. As a result of consuming too many purines and having a genetic susceptibility, people can develop hyperuricemia, which increases the risk of MSU crystals nucleating in their joints [5].

Uric acid can be converted in the majority of species to highly soluble allantoin or even to ammonia. After the genetic loss of uricase, the uric acid catabolic enzyme that converts uric acid to allantoinic acid, gout is a disorder developed in humans and other primates. The kidney also filters uric acid, but by reuptake, it recovers the majority of the filtered burden. This continual attempt to prevent the elimination of metabolic "waste" may be the cause of various rewards linked to high uric acid levels [6].

It is believed that urate concentration as well as other variables have a role in the overall physicochemical process of MSU crystallization, which is similar to the production of other crystals. Plasma seems saturated with urate when it approaches the solubility limit, which is usually 6.8 mg/dl (405 mol/L), as previously mentioned. The solution is regarded as supersaturated when it exceeds this concentration. In the supersaturation range, the solubility of urate is changed further to initiate the production of MSU crystals, and depending on the local environment, crystallization progresses further. Through its influence on urate solubility, the temperature is another environmental component that might contribute to the production of MSU crystals.

After they have developed, MSU crystals cause local tissue macrophages to produce inflammatory cytokines including IL1. These mediators trigger a neutrophilic influx, which is the typical pathophysiological hallmark of acute gout, together with a complement that is directly triggered at MSU crystal surfaces. The crystals that neutrophils come into contact with during infiltration cause them to become even more activated, resulting in the production of more proinflammatory mediators like the arachidonic acid derivatives PGE2 and LTB4 [7].



**Fig 2: Metabolic pathway of nucleotides**

**III. PATHOGENESIS**

*i) The inflammasome and pattern recognition receptors in gout:*

Toll-like receptors, NOD-like receptors and inflammasome, retinoic acid-inducible gene I-like receptors, C-type lectin receptors, and absence in melanoma 2-like receptors are the five main groups of PRRs. Mammalian PRRs have two possible subcellular localizations: membrane-bound or cytoplasmic. Even though immune cells like macrophages and dendritic cells express PRRs in large quantities, nonimmune cells like vascular cells that may indirectly control inflammatory responses also do so [8].

Toll-like receptors, NOD-like receptors, and inflammasomes play significant roles in gout among these recognition receptors.

Caspase 1 can be activated by a variety of inflammasomes, all of which contain proteins from the NOD-like receptor family [9]. Under the stimulation of NLRP3 activators alone, NLRP3 inflammasome activation in macrophages is either not observed at all or detected only weakly, whereas pretreatment with microbial ligands or endogenous cytokines substantially stimulates NLRP3 inflammasome activation. This pre-treatment, also known as the "priming signal," acts as the initial signal to initiate the activation of the NLRP3 inflammasome in innate immune cells.

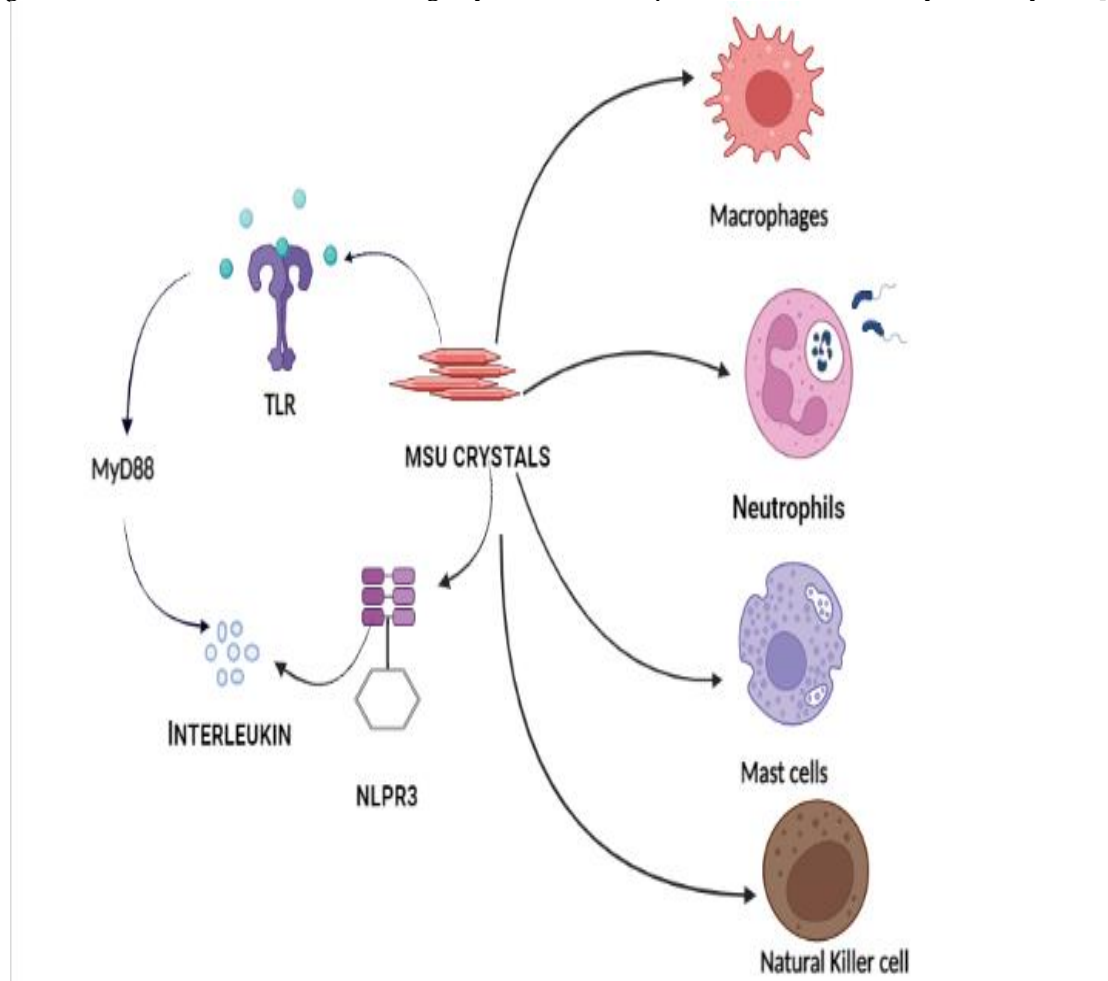
Different danger signals, such as DAMPs and PAMPs, prime the licensing of NLRP3 and then cause the assembly and activation of the NLRP3 inflammasome. Cellular stressors and particulate crystals, among other stimuli, can activate NLRP3 which has been programmed to respond. It has been suggested that secondary signaling processes such as K<sup>+</sup> efflux and Ca<sup>2+</sup> mobilization, lysosomal instability, and ROS generation which activate NLRP3 inflammasome, which is induced by a variety of NLRP3 stimulators [10].

The cause of gout has been known for more than a century, but the mechanisms causing inflammation brought on by MSU crystals have just lately started to be recognized. Although significant neutrophil infiltration into the synovium and joint fluid is the pathological hallmark of a gout attack, neutrophils are not present in a healthy joint. Therefore, the primary event after MSU crystals have precipitated within the joint is thought to be the interaction of MSU crystals with resident joint cells, primarily the synovial lining cells, which in turn drives neutrophil infiltration [11].

Inflammasome activation, altered innate immunity, and elevated IL-1 production has all been linked to gout. Leukocyte activation by MSU crystals is the primary cause of gouty inflammation. MSU crystals function as DAMPs in gout and can be detected by TLRs, specifically TLR2 and TLR4. Similar to what was previously mentioned, NLRP3 activation generally follows the same pattern. By cleaving their respective precursors, pro-IL-1 and pro-IL-18, caspase-1 activates IL-1 and IL-18. Additionally, pyroptosis and necroptosis have been linked to gout among other types of cell death. Pyroptosis, as opposed to apoptosis, results in the release of cytosolic material that is loaded with a variety of pro-inflammatory mediators. Additionally, receptor-interacting serine/threonine protein kinase 3 (RIPK3) and mixed lineage kinase domain-like protein (MLKL)-dependent pathways may be activated by MSU crystals to cause necroptosis [12].

Toll-like receptors are essential sensors of infectious and dangerous signals on leucocytes. They are a crucial component of the innate immune system, and it has become increasingly obvious how they contribute to the development of inflammatory diseases. MSU crystals could be a danger signal generated by damaged cells that activates TLRs to start innate immune responses [13].

The function of TLRs in the pathophysiology of inflammatory diseases has become increasingly clear. According to reports, MSU interacts with the PRRs, TLR2, TLR4, and cell surface adaptor CD14. This activation of MyD88-dependent signaling encourages the release of cytokines and the infiltration of neutrophils. TLR2 is assumed to be a dominant component in determining the degree of inflammation and the course of gouty arthritis development since it can identify MSU crystals [14].



**Fig 3: Pattern recognition receptor and inflammasome in gouty arthritis**

*ii) Diet:*

As a consequence, gout and hyperuricemia are viewed as diseases related to lifestyle. Epidemiological studies conducted over the past ten years have shown a correlation between the consumption of purine-rich meals and the serum concentration of uric acid, which is higher in people who frequently consume significant amounts of purine-rich foods than in people who don't. Additionally, it has been observed that eating these foods may increase your risk of developing gout [15].

High protein intake and a variety of purine-rich meals have long been considered gout risk factors. Similarly, to this, studies on the metabolism have suggested that eating dairy products may play a part in preventing gout. An increased risk of gout was linked to eating more meat and shellfish [16].

When consumed alcohol alone or with a meal high in purines, alcohol has a higher impact on blood urate levels than a diet high in purines. Many patients are aware that feasts heavy in alcoholic beverages and purine-rich meals often lead to gout attacks. Acute alcoholic overconsumption results in transient lactic acidosis decreased renal urate excretion and a worsening of hyperuricemia. Chronic alcohol consumption increases the generation of purines by increasing the breakdown of adenosine triphosphate to adenosine monophosphate through the ethanol metabolism's conversion of acetate to acetyl CoA. Beer's purine content, notably the easily absorbed guanosine, has a higher impact on the generation of uric acid [17].

Humans obtain their purines from food (exogenous sources) and the conversion of nucleic acids into purine-containing nucleotides (endogenous sources). Brain, liver, heart, lung, kidney, viscera, duck meat extract/duck broth, goose, bird, corned beef, sardine, small shrimp, broth, alcohol, and yeast were among the foods with high purine concentration (> 100-1000mg/100g foodstuff) [18]. Additionally, a high-protein diet enhanced oxidative stress, which was accompanied by an increase in urate levels in the cerebral cortex and hypothalamus [19].

Urate levels significantly rise after consuming foods high in fructose, which increases the conversion of ATP to AMP, a precursor to uric acid, and after consuming a lot of purines.

It is generally known that eating purine-rich meals frequently, especially those of animal origin, increases the risk of developing gout [20].

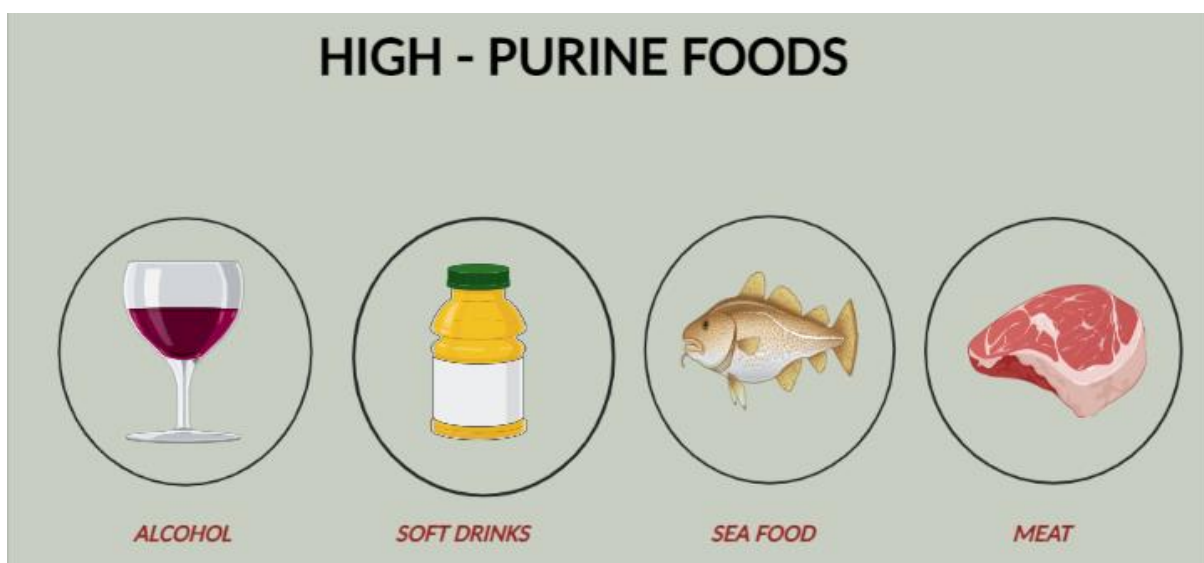
Animal purine sources had a significantly bigger influence than plant purine sources. Especially for meals of animal origin, avoiding or consuming fewer purine-rich foods may help lower the incidence of recurring gout attacks [21].

Numerous biological explanations have been put out to explain how drinking alcohol increases the likelihood of developing incident gout. Alcohol consumption speeds up the liver's breakdown of adenosine triphosphate and increases the creation of urate, according to studies. Another potential explanatory element linked to an increased risk of gout attacks is the high purine content in some alcoholic beverages, such as beer [22].

Nowadays, fructose is frequently used as a sweetener, especially in the form of high-fructose corn syrup. Even though fructose is not a purine, fructose phosphorylation uses up ATP at a rate that causes extra adenine to be released, which eventually turns into uric acid. Lentils, peas, and poppy seeds were among the foods to stay away too.

The main "ketone bodies" formed during typical fatty acid catabolism are acetoacetate and hydroxybutyrate, both of which have been demonstrated to reduce uric acid excretion.

This is true for lipids that are consumed outside of the body as well as fat that has been mobilized from adipose tissue, however, the ketone burden is often negligible. When hepatic glycogen levels are low and the body switches to using tissue fat as its main energy source during a fast, this factor becomes clinically significant. Fasting used to be a narrow therapeutic option for morbid obesity, but it quickly lost favour due to complications like hyperuricemia and gout. Modern low-carbohydrate diets for obesity have raised questions about whether less-dramatic ketogenic diets can help treat people with hyperuricemia brought on by ketosis. The primary objective of "low-carb" diets is to mobilize extra fat reserves, which cannot be done without ketone body generation. Fortunately, this hypothetical worry has not manifested in real life, and successful weight loss is linked to an increase rather than a decrease in the serum urate level [23].



**Fig 4: High purine foods augment the risk of gouty arthritis**



*iii) Transporters responsible for gout:**a. ABCG2*

Human urate homeostasis is a complicated and highly heritable process that includes renal urate reabsorption, metabolic urate production, and renal and extrarenal urate excretion. Moreover, alterations in urate excretion are frequently the main reason for hyperuricemia and gout. The majority of urate is removed through glomerular filtration in the kidney, which is followed by an interaction of several transporters engaged in reabsorbing or excreting urate in the succeeding parts of the nephron that is still not fully understood. In this setting, genome-wide association studies and subsequent functional investigations have exposed the significance of single nucleotide polymorphisms in the etiology of hyperuricemia and early-onset gout and identified the ATP-binding cassette transporter (ABCG2) as a key urate transporter.

A multi-drug efflux pump known as ABCG2 (sometimes referred to as BCRP) has been shown to support transport mechanisms in a variety of tissues and cell types. It can transport a range of substrates across the membrane and is a member of the ABC transporter superfamily. The polar epithelial cells of the gut and kidney as well as the cerebral blood-brain barrier and canalicular membrane of the liver may all be found at the entry and exit points of the human body. ABCG2 is also strongly expressed in the placental syncytiotrophoblasts [24].

A genome-wide linkage analysis of gout showed that the adenosine 5'-triphosphate-binding cassette, subfamily G, member 2 genes ABCG2/BCRP are located in a gout-susceptibility locus on chromosome 4q (25). It is one of 48 human ABC transporters that make form a superfamily that transports a variety of substrates and is activated by ATP binding [26]. A urate transporter that is encoded by the ABCG2 gene affects serum urate levels and gout risk. It has been demonstrated to be among the most potent risk factors for the onset of gout [27]. Both the kidney and the gut contain ABCG2, however, the kidney's expression is much weaker than the small intestines. Its function in secreting urate into the gut is supported by numerous lines of evidence. Renal urate excretion is increased in hyperuricemia, which is connected with the ABCG2 risk gene. This is consistent with both an indirect influence on the kidney and a direct effect on intestinal clearance [28].

*b. URAT:*

About 90% of the urate that the kidney filters each day is reabsorbed and this action is regulated by certain transporters. Urate Transporter-1, a urate-anion exchanger located on the luminal side of the proximal renal tubule, is the main transporter. The primary mechanism for the reabsorption of urate in the human kidney is URAT-1, which belongs to the family of organic anion transporters. Gout and hyperuricemia are linked to URAT-1 gene mutations [29].

Proximal renal tubule transporters, such as URAT1 (encoded by the SLC22A12 gene), a member of the major facilitator superfamily, are responsible for reabsorption in humans. Secondary carriers belonging to the major facilitator superfamily can transport small molecule solutes along chemiosmotic ion gradients. URAT1 is expressed on the apical surface of the proximal renal tubules, facing the lumen, where it exchanges intracellular anions for filtered urate, in contrast to the basolateral transporter, which transports urate through to the interstitial fluid and blood [30].

Other mammals like rabbits and pigs, which primarily secrete urate, are likely lacking URAT1. However, urate secretion is likely minimal in humans, and URAT1 is believed to be the main mechanism for controlling blood urate levels [31].

The identification of other putative urate transporters has been made easier by the discovery of URAT1, a crucial molecule in renal urate management. As a result, it has also been demonstrated that other OATs, including OAT1, OAT3, OAT4, OATv1/NPT1, UAT, and MRP4, transport urate. Despite having a strong attraction for monovalent endogenous and exogenous anions such as nicotinate and pyrazine, which are known to interfere with renal uric acid transport, URAT1 is also highly selective for urate. It has been demonstrated that these endogenous and exogenous anions and URAT1 exchange urate [32].

Recently, genes that control urate transport have drawn a lot of attention. Human urate transporter 1, a member of the family of organic anion transporters that, along with other recently discovered transporters, is crucial in regulating uric acid reabsorption from the renal tubules, is encoded by the SLC22A12 gene. This gene's polymorphism has been linked to hyperuricemia and the "under-excretion" of uric acid [33].

Lack of functioning URAT1 transporters has some negative effects, including greater urine and lower blood urate levels, which are linked to crystal formation in the renal tubules. Additional research has demonstrated that hyperuricemia can aggravate proteinuria and renal impairment by accelerating vascular lesions and glomerular hypertension [34].

*c. OAT:*

The highly polarised epithelial cells that make up the renal proximal and distal tubules are responsible for the specifically directed transport of different solutes. This kidney function is accomplished by the intimate pairing of apical and basolateral carriers expressed in the renal epithelial cells, which is crucial for maintaining homeostasis in the body. The family of organic anion transporters (OATs), which are expressed in the renal epithelial cells to control the excretion and reabsorption of endogenous and foreign organic anions, belongs to the major facilitator superfamily (SLC22A) [35].

Drugs and environmental toxins are discharged into the urine, especially from the kidney. Transporters of OAs, often referred to as organic anion transporters (OATs), are crucial in controlling the pharmacokinetics and pharmacodynamics of medicines, among other features [36].

The OAT family transports a wide range of substrates, such as NSAIDs, metabolites, and antibiotics (including urate). OAT1 and OAT3 are thought to mediate urate and drug uptake from the blood into the proximal tubule cell via anion exchange for eventual secretion at the apical membrane. OAT1 and OAT3 are found on the basolateral membrane of the renal proximal tubule cell [37]. In human kidney samples, OAT1, OAT2, OAT3, OAT4, OAT10, and URAT1 have all been found [38].

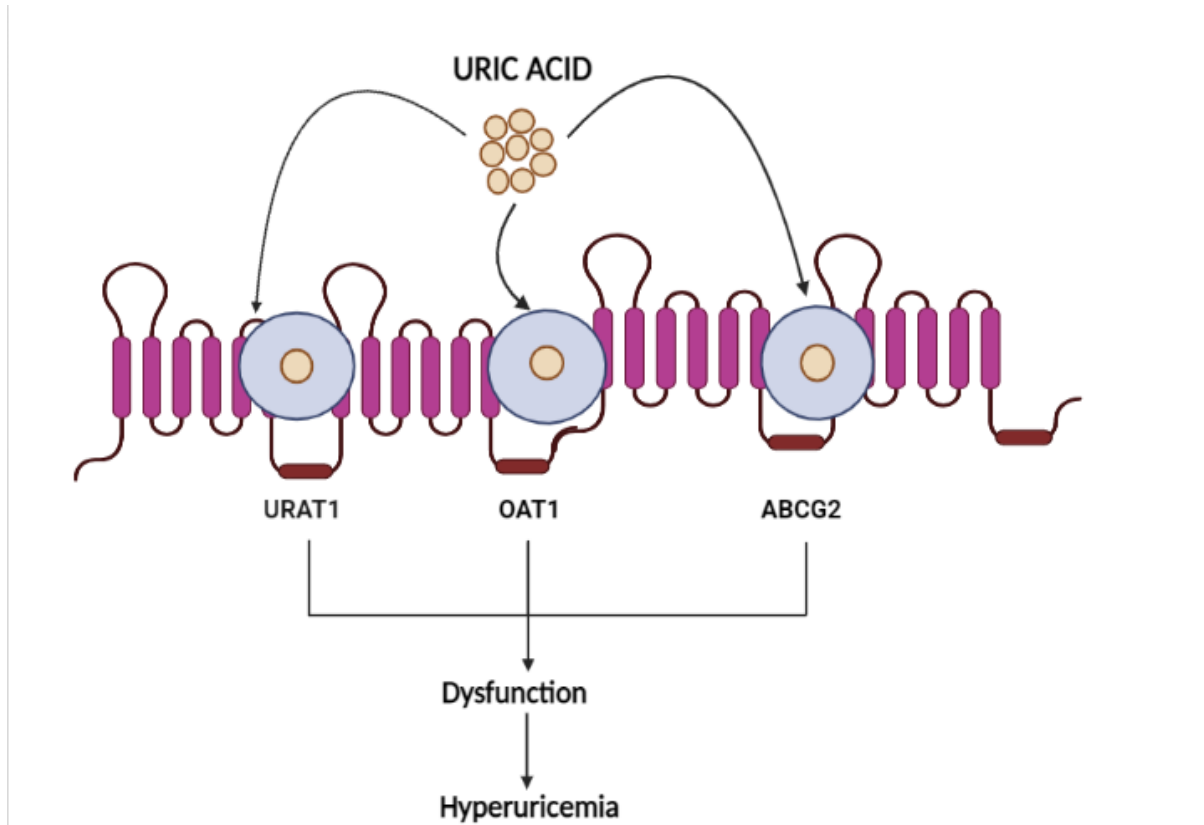
OAT4 is a multispecific anion transporter that is expressed in the apical membrane of epithelial cells originating from the proximal tubule and is encoded by the SLC22A11 gene. It utilizes a process that is transactivated by intracellular dicarboxylates to participate in luminal urate reabsorption [39].

Although there are more OAT isoforms than ever before, it appears likely that OAT3 also engages in urate transport. OAT3's human homolog has been cloned, and only faint bands of its mRNA have been found in the brain and skeletal muscle. It is primarily expressed in the kidney [40].

OAT1 and OAT3, which take part in organic anion/dicarboxylate exchange, are the two OAT transporters in humans that have been most thoroughly researched [41].

OAT1 and OAT3 may be crucial in the etiology of hyperuricemia [42].

The uric acid levels are controlled by SLC22A6 (OAT1) and SLC22A8 (OAT3); some mutations are linked to altered uric acid levels, gout, and kidney stones [43].



**Fig 5: Transporters dysfunction leads to gouty arthritis**

*iv. HGPRT deficiency:*

Glucose-6-phosphatase deficiency, severe and partial hypoxanthine-guanine phosphoribosyltransferase deficiency, and increased 5'-phosphoribosyl-1'-pyrophosphate synthetase activity are three hereditary abnormalities that cause the early development of severe hyperuricemia and gout [44].

Using Edman degradation and carboxypeptidase digestion, the amino acid sequence of the purified HPRT protein from human erythrocytes was established. They discovered that the human HPRT protein has 217 amino acids and a molecular weight of 24.47 kDa. These were the following estimations of the actual subunit molecular weight of 26 and 24.5 kDa from SDS-polyacrylamide gel electrophoresis. Like many other soluble cytoplasmic enzymes, HPRT has an acetylated N-terminal alanine, and the protein resides as a tetramer of identical subunits in the cytoplasm. All cells contain HPRT, however, the basal ganglia have the highest amount of activity. The substrates for the enzyme include guanine, hypoxanthine, and PRPP [45].

Gout and hyperuricemia are known to be caused by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency [46].

Urate nephropathy, uric acid urolithiasis, bladder calculi, and severe gouty arthritis are among the systemic effects of hyperuricemia [47].

The gene for this enzyme is found on the long arm of the X chromosome, and it catalyzes the transfer of the phosphoribosyl moiety of PP-ribose-P to hypoxanthine and guanine to generate IMP and GMP, respectively (Xq26-q27.2). A cytoplasmic enzyme, HPRT is most active in the testicles and brain. The gross overproduction of uric acid that results from the inability to recycle either hypoxanthine or guanine in subjects genetically deficient in this enzyme, causing a lack of feedback control of synthesis along with rapid catabolism to uric acid, illustrates its significance in the normal interplay between synthesis and salvage [48].

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is a purine metabolism inborn defect linked to excessive uric acid generation. All HPRT-deficient patients have excess uric acid production, which is linked to gout and lithiasis. The HPRT gene mutation can result in a deficiency in the activity of the HPRT enzyme [49], which causes a build-up of the substrates hypoxanthine and guanine, which xanthine oxidase then uses to convert to uric acid. Enzymatic tests are required to confirm HPRT deficiency. Patients have adenine phosphoribosyltransferase activity that is elevated and low or zero HPRT activity in their hemolysates. A single structural gene that spans roughly 45 Kb on the long arm of the X chromosome at Xq26 and is responsible for encoding human HPRT has nine exons and a 654 bp coding region. The majority of HPRT-deficient patients exhibit HPRT mRNA expression, and cDNA sequencing can be used to provide a molecular diagnosis. Genomic DNA sequencing might be

required in other circumstances. Deletions, insertions, duplications, and point mutations have been identified as the cause of HPRT deficiency. These mutations exhibit a great degree of variation in form and location within the gene [50].

#### IV. CONCLUSION:

The pathogenesis of gout involves the activation of the NLRP3-IL-1 axis, which is an autoinflammatory condition. More specialized treatment plans for gout that focus on the autoinflammatory process are still needed. Gout was considered a disease of the privileged for many years. Gout eventually declined and was referred to as a "lost disease" in the early 20th century. But throughout the latter half of the 20th century, gout incidence grew along with rising alcohol, fructose, and obesity rates increases that are probably connected. Consumption of purine-rich foods is linked to both incident and acute gout events. Gout can result from long-term purine ingestion because it raises urate levels.

A thorough understanding of the etiology of hyperuricemia and gout is made possible by genomic studies on uric acid metabolism. In general, alterations at the gene level contribute to the onset and progression of the disease. Therefore, a key component of our future research will continue to be the study of hyperuricemia and gout at the gene level. The early diagnosis and prevention of gouty arthritis will benefit greatly from the identification of the extremely specific and sensitive gene markers of elevated serum uric acid levels. Understanding gout and subsequently managing it has been difficult for doctors throughout medical history over the past ten years. These systems are now much more understood, and medicines that target these pathways have already been found or developed the majority of them with favorable pharmacokinetic features.

#### V. ACKNOWLEDGEMENT:

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## VII. ABBREVIATIONS:

DNA- Deoxyribonucleic acid

RNA- Ribonucleic acid

MSU- Monosodium urate crystal

IL 1- Interleukin 1

PGE2- Prostaglandin E2

LTB4- Leukotriene B4

APRT: Adenine phosphoribosyl transferase

GPRT: Guanine phosphoribosyl transferase

AD: Adenine deaminase

GD: Guanine deaminase

PNP: Purine nucleoside phosphorylase

XO: Xanthine oxidase

PRR- Pattern recognition receptor

NLRP3- NACHT, LRR, and PYD-domains-containing protein 3



PAMP- pathogen-associated molecular pattern  
DAMP- damage-associated molecular pattern  
TLR- Toll-like receptor  
ROS- Reactive Oxygen species  
CD14- Cluster of differentiation 14  
MyD88- Myeloid differentiation primary response 88  
ATP- Adenosine triphosphate  
AMP- Adenosine monophosphate  
BCRP- Breast cancer resistance protein  
ABC- ATP-binding cassette  
OAT- Organic Anion transporter  
NPT1- Sodium- dependent phosphate cotransporter 1  
MRP4- Multidrug resistance protein 4  
NSAIDs- Non- steroidal anti-inflammatory drugs  
IMP- Inosine monophosphate  
GMP- Guanosine monophosphate  
cDNA- Complementary DNA