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Hyperuricemia and Gout:
A Prevalent and Chronic Disease

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Educational Objectives

At the completion of this activity, the participant should be able to:

- Summarize the epidemiology of hyperuricemia and gout
- Identify gout as a chronic disease by understanding the role of hyperuricemia in gout
- Explain the progressive nature of hyperuricemia and gout by discussing the advancement of the disease through the 4 stages

Program Completion Time

Based upon trials, the estimated time to complete this program is 1 hour.

Target Audience

This educational activity is intended for rheumatologists.

Commercial Support Acknowledgement

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Classically, gout has been perceived as an acute disorder of the big toe, which affects people who have unhealthy lifestyle habits, such as too much eating or drinking. Information on the pathophysiology, clinical manifestations, and epidemiology of gout suggest that, in order to diagnose and manage this disease appropriately, a new perspective is necessary.

Gout is actually a chronic disease due to its underlying cause, uncontrolled hyperuricemia. Once a patient presents with an acute flare, they are at risk for subsequent clinical manifestations until the underlying cause is corrected. Furthermore, acute attacks of the big toe are only one of the many ways gout can present clinically. Manifestations range from early, hidden damage, resulting from silent tissue deposition of urate deposits, to advanced, debilitating complications, such as chronic arthritis. This, combined with the fact that a growing body of evidence demonstrates an increasing incidence and prevalence of this disease, emphasizes the need for an accurate understanding of gout by clinicians.

THE INCREASING INCIDENCE AND PREVALENCE OF GOUT

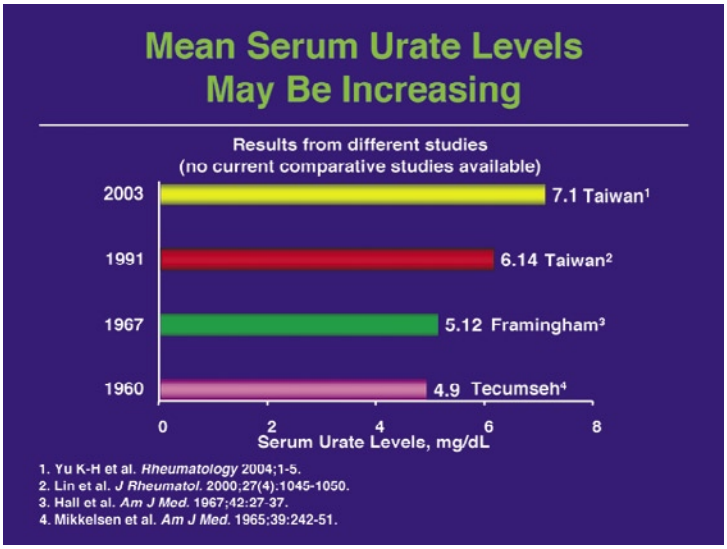
Gout is a disease that has been around for centuries, with famous sufferers that include Henry VIII, Benjamin Franklin, and Leonardo da Vinci.[1] Therefore, it would be reasonable to assume that, over time, a vast array of knowledge about this disease has been accumulating, and the ultimate result would be effective control of gout. The increasing epidemiology data on gout demonstrates that this may not be the case.

Gout Is on the Rise

Incidence data on gout is limited because it is difficult to accurately measure data on a chronic disease that is diagnosed based on acute episodes.[2] Some information is available, however, such as that obtained from the Rochester Epidemiology Project computerized medical record system. After analyzing these records, it was observed that 18 new cases of primary gout (gout without a history of diuretic use) were diagnosed between 1977 and 1978, and 60 new cases were diagnosed between 1995 and 1996. After adjusting the annual incidence rate for age and sex, it was found that the rate of primary gout had significantly increased greater than 2-fold (P<.001) over these 2 decades.[3]

There are also limitations to obtaining prevalence data on gout, since self reports, rather than prospective studies, are usually used to gather this information. Nonetheless, available data indicates that the prevalence of gout is high and increasing. Gout is the most common inflammatory joint disease in men over 40 years of age[4] and is thought to affect more than 5 million Americans between 1988 and 1994.[5] This figure for gout may be even greater today, as a study by Wallace and colleagues demonstrated that the number of cases increased from 2.9 per 1000 in 1990 to 5.2 per 1000 in 1999.[6]

The increasing prevalence of hyperuricemia, the underlying cause of gout, is no doubt a contributor to the increase in gout.[7-10] The physiochemical definition of hyperuricemia is any concentration of serum urate at or above approximately 6.8 mg/dL, in which urate is no longer soluble and crystallization may occur.[11] Results from studies performed in 1960, 1967, 1991, and 2004 suggest that an increasing number of people fit the definition for hyperuricemia. Although this information was not obtained by a single, long-term follow-up study, this does provide strong support for the view that serum urate levels are increasing in the general population.[7-10]

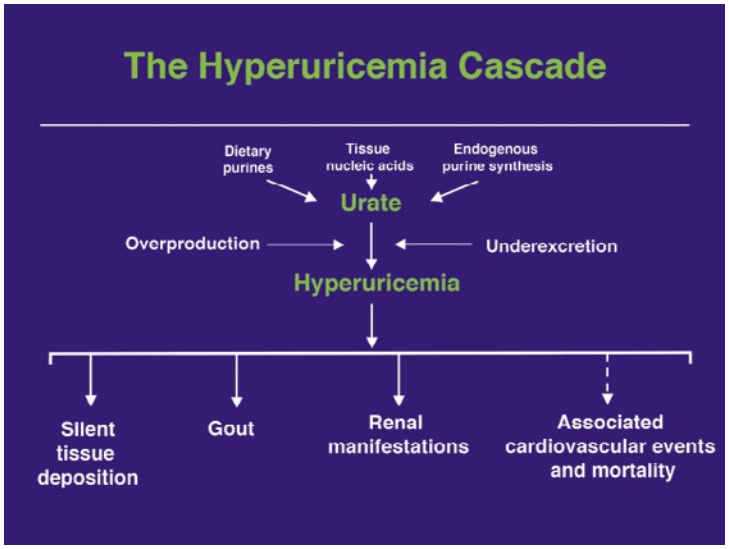


GOUT IS A CHRONIC DISEASE

Understanding that gout is a chronic disease, and treating it as such, may assist in curtailing the increasing number of individuals suffering from it. Gout is chronic because the underlying metabolic disorder that leads to gout is hyperuricemia. If hyperuricemia is left uncontrolled, the underlying cause of gout will continue to be present, even in the absence of apparent clinical manifestations of gout. Appreciating the relationships among uric acid (urate), hyperuricemia, and gout, and linking these relationships to the progression of the clinical manifestations of gout, will make it apparent that gout is a chronic disease.

The Hyperuricemia Cascade

Uric acid (urate), hyperuricemia, and gout can be linked through a cascade of physiologic events.



The urate, or ionized form of uric acid, is the end product of purine metabolism in humans and exists at a higher pH, such as those of extracellular fluids, like serum. Uric acid is un-ionized and occurs at acidic pH levels, such as that of the urine.[12]

When serum urate is overproduced or underexcreted, and the concentration meets or exceeds the limit of solubility (a concentration of approximately 6.8 mg/dL), hyperuricemia occurs.[12] The development of hyperuricemia can lead to multiple diseases and, in the case of gout, this supersaturation of urate in extracellular spaces crystallizes and deposits in joints and soft tissues, initiating the clinical manifestations associated with this disease.[11] Each aspect of the hyperuricemia cascade is described in more detail below.

The Production and Elimination of Uric Acid

The normal production and elimination of uric acid needs to be defined in order to appreciate the abnormalities in these processes that lead to hyperuricemia and resultant gout. The degradation of purines from a variety of different sources, such as endogenous purine nucleotide synthesis, dietary purine intake, and purine salvage from nucleic acids of dead and dying cells, contributes to the production of urate.[11] In the final steps of degradation of purines, the purine bases hypoxanthine and xanthine are irreversibly oxidized to urate in reactions catalyzed by the enzyme xanthine oxidase.[13] Once produced, a small fraction of uric acid, equivalent to one third of the daily production, is eliminated via the gastrointestinal tract, while the remaining two thirds are eliminated through the kidney.[11]

Hyperuricemia: The Imbalance Between Urate Production and Elimination

An imbalance between urate production and elimination is likely to result in hyperuricemia. Patients with primary overproduction or underexcretion of uric acid usually have an idiopathic defect, which denotes that the cause of the condition is unknown or has arisen spontaneously. There are some exceptions to this, however, such as some well studied primary causes of overproduction of urate, including phosphoribosyl pyrophosphate (PRPP) synthetase overactivity and hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency. These conditions drive the synthesis of purines, which results in an increase in serum urate when these purines are degraded.[14,15]

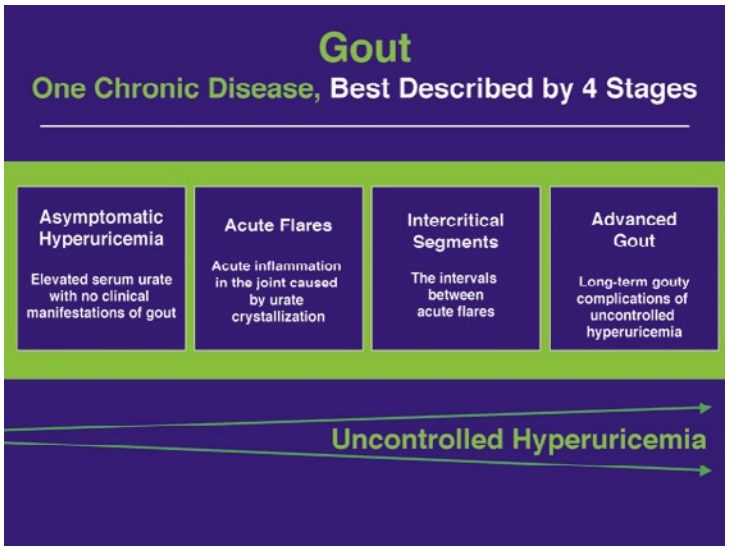
Patients with secondary hyperuricemia have impaired urate production or excretion as a result of identified contributing factors, such as a comorbid disease process or taking a specific drug. For example, a decrease in the excretion of urate occurs with thiazide diuretic therapy because this drug enhances reabsorption of urate in the proximal tubule. Overproduction can occur when there is an increase in the amount of dietary purine intake. This enhances the amount of purine compounds available for conversion to urate and can result in hyperuricemia.

Available information suggests that the imbalance between urate production and elimination, which results in hyperuricemia, is most often the result of impaired elimination of uric acid. Relative impairment of uric acid excretion may contribute to hyperuricemia in 80% to 90% of patients with gout.[11] Therefore, overproducers of urate constitute a small proportion of patients with this disease.

Gout Is a Result of Hyperuricemia

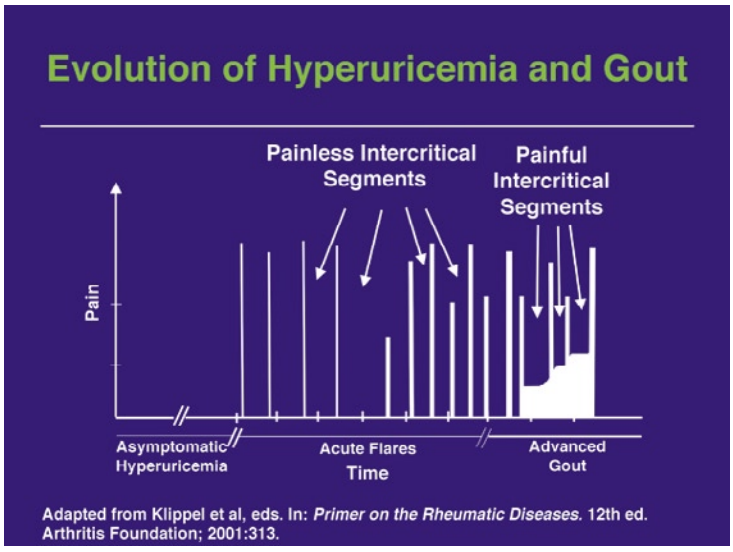
Gout occurs when the monosodium urate crystals formed during the hyperuricemic state precipitate in joints and soft tissues, resulting in the clinical manifestations associated with this disease.

Although gout is often described as having 4 stages, it is a single chronic, progressive disease.



Linking these stages together into 1 disease, as depicted by the green background in the figure, is uncontrolled hyperuricemia. These 4 stages are commonly referred to as asymptomatic hyperuricemia, acute flares, intercritical segments, and advanced gout.

Diseases are considered chronic when they are of long duration and gradual onset. These characteristics certainly apply to gout when observing the progression of this disease through the 4 stages. The "Evolution of Hyperuricemia and Gout" figure demonstrates this progression, with the y-axis indicating pain and the x-axis indicating time.



Adapted from Klippel et al, eds. In: *Primer on the Rheumatic Diseases.* 12th ed. Arthritis Foundation; 2001:313.

Gout begins with asymptomatic hyperuricemia and resultant silent tissue deposition of urate deposits in some individuals, potentially resulting in hidden damage. This damage is considered hidden because no apparent clinical manifestations of gout are present during this time, as indicated by the figure. If the underlying hyperuricemia is left uncontrolled, the deposition of urate crystals increases over time, as does the risk of developing a clinical manifestation of gout, such as an acute flare (the vertical bars in the figure).[16]

Over time, the expanding total body urate load causes the clinical manifestations of gout to gradually escalate in severity, eventually resulting in the advanced stage of the disease for some individuals. This is depicted in the "Evolution of Hyperuricemia and Gout" figure by the vertical bars, indicating acute flares of gout, which increase in number and start occurring closer together as the disease progresses. Also in the advanced stages, continued urate deposition in the joints may progress to chronic arthritis, which manifests as persistent pain and stiffness (indicated by the shaded section of the figure). Acute flares can be superimposed on top of this condition.[16]

Although flares present acutely, with a rapid onset of severe symptoms that occur for a brief duration, the underlying reason for these flares is a chronic problem. Patients with uncontrolled hyperuricemia and gout still have the disease even when the acute flare subsides. The acute flares, as well as the other stages of gout, are described below in greater detail.

THE 4 STAGES OF GOUT
The Range of Progressive Manifestations

The urate deposits, which reflect the uncontrolled hyperuricemia, accumulate and clinically manifest in a variety of ways. Therefore, the stereotypical inflamed big toe as a presentation of gout may not always be the case. For clinicians diagnosing and treating gout, understanding that uncontrolled hyperuricemia is the underlying cause of gout is important, but so is awareness of the variety of ways in which urate deposits may lead to progressive clinical symptoms.

Asymptomatic Hyperuricemia: The Beginning of Silent Tissue Deposition

Asymptomatic hyperuricemia is the first stage of gout. This stage has been artificially termed "asymptomatic" because it is characterized by elevated serum urate with clinically unapparent gout. Patients may have asymptomatic hyperuricemia for years before ever experiencing a clinical manifestation of gout. Although no clinical signs are present, the uncontrolled hyperuricemia may result in urate crystal formation and deposition in many subjects,

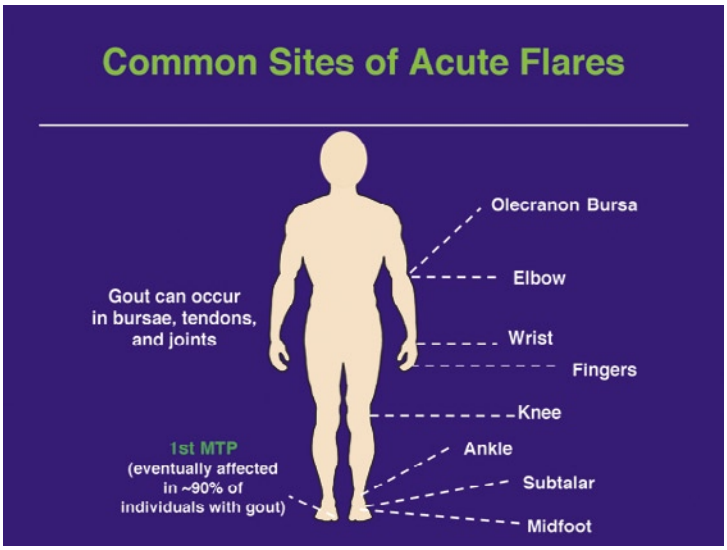
with gradual accumulation in joints and soft tissues. This "silent" tissue deposition may cause hidden (clinically unapparent) damage to these areas. For example, silent tissue depositions in the form of microtophi have been observed in the joints of patients presenting with their first acute flare. These microtophi are thought to antedate the attacks of inflammation.

Because the development of clinical gout is a reflection of the accumulation of urate in the joints and soft tissues, the length of time that the asymptomatic hyperuricemia is present reflects the likelihood of this occurrence. This explains, in part, why older individuals experience gout more frequently, as the sustained tissue deposition of urate may have been occurring for years in these patients.[17] The degree of elevated serum urate levels also predicts the probability of developing clinical gout. The Normative Aging Study, a 15-year, prospective trial, found that the higher the initial serum urate level in men that had asymptomatic hyperuricemia, the greater the chances of a first acute flare.[18]

Acute Flares

Typically, the initial symptomatic stage of gout is the acute flare, which is a result of urate crystals in the joints stimulating the release of numerous inflammatory mediators. The acute flare usually presents during the evening with an abrupt onset of severe joint inflammation, warmth, swelling, erythema, and pain. The severity of pain associated with the flare may vary from mild twinges to pain so intense that the joint cannot be touched. Systemic symptoms, such as fever, chills, and malaise, may also occur and are the result of some of the inflammatory mediators leaking into the venous circulation.

The initial attacks of gout are usually experienced in the lower extremities and are typically monoarticular. An acute flare at the first metatarsophalangeal (MTP) joint, known podagra, is the most common site of an acute flare. Podagra occurs in 80% of patients with gout, and 50% of patients experience their first acute flare in this joint. However, patients who present with symptoms in alternate joints, such as the ankles, tarsal and other metatarsal joints, knees, and elbows, should also be evaluated for gout.[19] Gout can also occur in bursae and tendons.



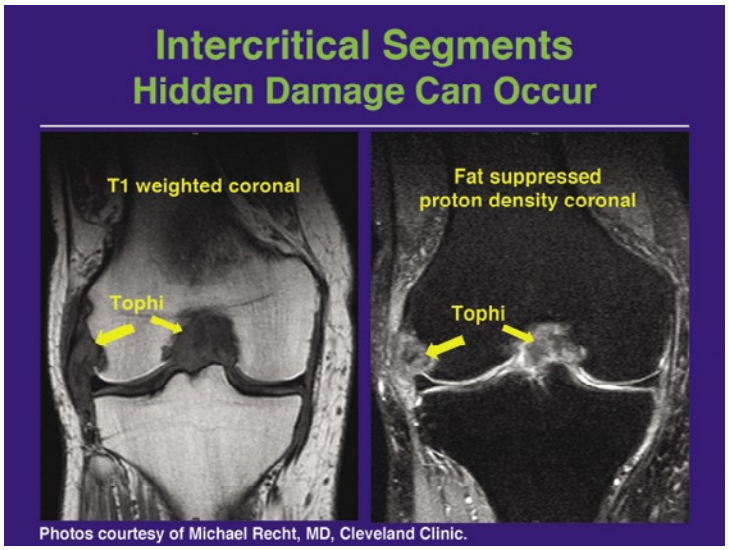
Acute flares can last from several hours to several weeks. Typically, the initial acute flares subside over 3 to 10 days in the absence of pharmacologic therapy.[16] This happens because, in the final stages, a variety of mechanisms are initiated that lead to eventual spontaneous resolution. These mechanisms include an increase in the amount of anti-inflammatory mediators and, conversely, the degradation of inflammatory mediators.[17] It must be taken into consideration that, even though the flare has subsided, the patient is not cured of this chronic disease. Following the first acute flare, 66% of patients will experience a second flare within 1 year. Furthermore, once clinical gout is established, these flares become more frequent if the disease remains untreated.[20]

Intercritical Segments

A patient who experiences an acute flare is considered to be a gout patient no longer in the asymptomatic hyperuricemia stage. After this has occurred and the flare has resolved, the patient is in the intercritical stage, or the gout is clinically inactive. Although the disease is quiet during this stage, hyperuricemia is still present and the disease continues to advance if the elevated serum urate is left untreated. As the disease progresses, these intercritical segments will shorten due to the increasing frequency of flares, which reflect increasing body urate.[16]

Another indicator of uncontrolled hyperuricemia and progression of gout during this stage is the presence of urate crystals in the joints, even though symptoms are clinically absent. These crystals have been identified in joints where acute flares have occurred but were asymptomatic at the time.[21,22] Crystals have also been found in never-inflamed joints in patients with gout.[23-25]

The presence of these crystals throughout the body may contribute to some of the hidden damage that has occurred as a result of the continued silent tissue deposition. An example of this is visible from the magnetic resonance images (MRI) from a gout patient who visited the rheumatologist during an intercritical segment with the chief complaint of limited range of motion of the knee. This MRI was performed in order to confirm the anticipated cause of the clinical problem, which was thought to be a meniscus tear. However, the MRI indicated a tophus in the bone of the knee (lateral femoral condyle and intercondylar notch). Apparently, uncontrolled hyperuricemia resulted in urate deposition in the knee, forming a tophus and causing joint destruction and compromised mobility. This urate deposition was clinically silent from the perspective of acute flares. (Patient case study courtesy of Michael Recht, Cleveland Clinic.)

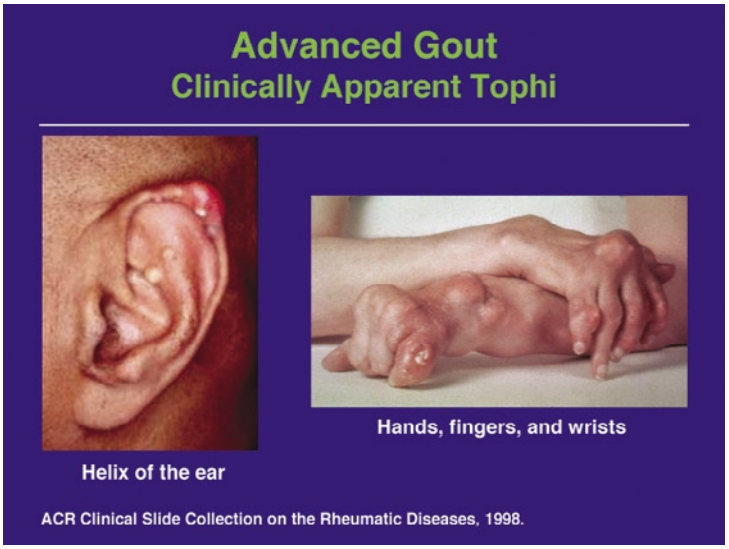


Advanced Gout

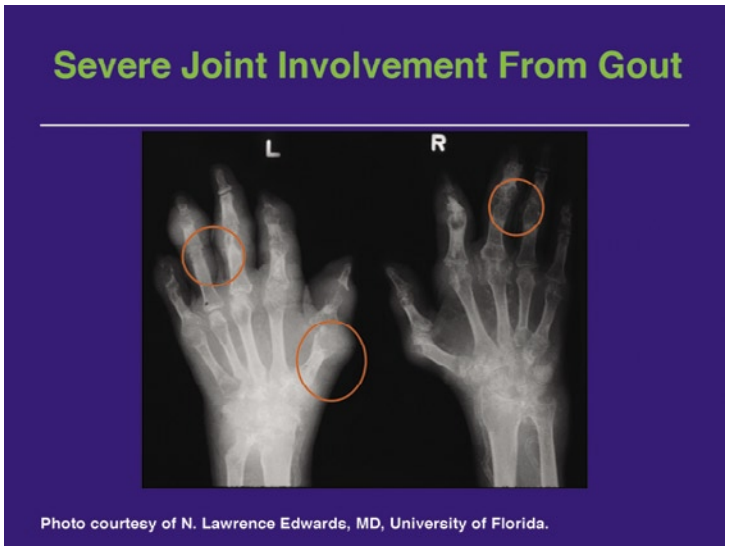
Patients who progress to the stages of advanced gout commonly experience clinical manifestations of the disease that go far beyond the acute inflammation in joints, bursae, and tendons. These advanced manifestations include chronic arthritis, tophi, and remarkable radiographic findings that were not visible early in the disease. Acute flares continue, however, and are characteristically longer in duration and may become polyarticular and involve the upper extremities.[16] The development of these advanced stages of gout usually occurs later in the disease, but this may not always be the case. For example, transplant patients on cyclosporine develop advanced manifestations, such as tophi and polyarticular flares, early in the course of the disease.[17]

The progression of chronic arthritis in advanced gout is a result of the increased amount of urate producing a burden in the joints that will have a functional impact. Chronic arthritis causes constant pain in the joints, which is uncomfortable for the patient, even during the intercritical segments. This pain is generally much less intense than the pain experienced during an acute flare.[16]

Advanced gout is often referred to as chronic tophaceous gout, to indicate the presence of tophi. This term needs to be interpreted with caution because, as previously emphasized, gout is a disease that is chronic, regardless of the stage. Tophi are masses of urate crystals deposited in the soft tissues, which can clinically manifest as pain, soft tissue damage and deformity, and joint destruction.[26] Tophi most commonly develop on the elbows, other periarticular regions, Achilles tendons, and, less often, the helix of the ear. Many tophi are clinically apparent, but this may not always be the case, since microtophi are suspected to form in the early stages of gout.



Bone and joint abnormalities are also apparent on plain radiographs and are indicative of the deposition of urate crystals. The radiographic changes, or gouty erosions, typically seen with advanced gout are both destructive and hypertrophic, leading to "overhanging edges."[16]



These overhanging edges are indicated by the orange circles on this radiograph from a gout patient. These radiographic changes associated with gout are distinct from the erosive changes associated with other rheumatic diseases.

CONCLUSIONS

The increasing epidemiologic data on gout indicate that adequate attention needs to be devoted to this disease. Understanding that the disease process that leads to gout is hyperuricemia, and appreciating that this is the reason why the disease is chronic, is important for both diagnosing and treating the disease. Uncontrolled hyperuricemia causes gout to progress from clinically silent damage to more advanced and debilitating manifestations. Awareness of the different ways gout can progress throughout the disease's stages will assist clinicians in making accurate diagnoses, followed by appropriate treatment choices. ■

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Posttest Questions

1. Data obtained from the Rochester Epidemiology Project computerized medical record system found that the age- and sex-adjusted incidence rate of primary gout from 1977-1978 to 1995-1996 _____.

a) Increased by 2-fold
b) Decreased by 2-fold
c) Did not change
d) Was affected by diuretic use

2. According to NHANES III, how many individuals in the United States have gout?

a) 5,000
b) 500,000
c) 1,000,000
d) 5,000,000

3. The underlying cause of gout is:

a) Tophi
b) Acute flares
c) Hyperuricemia
d) Xanthine oxidase

4. Hyperuricemia is considered to begin at a serum urate level of:

a) 6.8 mg/dL
b) 7.5 mg/dL
c) 8.0 mg/dL
d) 9.0 mg/dL

5. Place the 4 stages of gout in order according to how the disease progresses in most individuals:

I. Acute flares
II. Advanced gout
III. Silent tissue deposition
IV. Intercritical segments

a) I, II, III, IV
b) III, I, IV, II
c) I, III, IV, II
d) Gout is not a progressive disease

6. Which of the following regarding acute flares is *false*?

a) Following the first acute flare, 66% of patients will experience a second flare within 1 year.
b) Acute flares are the only clinical manifestation of gout.
c) Acute flares can occur in other areas of the body besides the first MTP joint.
d) The patient usually experiences erythema and pain when they have an acute flare.

7. If a patient is in an intercritical segment:

a) They are cured of gout
b) They have never had an acute flare
c) Their joints are completely free of pain
d) Crystals may be present in their joints, causing hidden damage

8. The clinical manifestations of gout experienced during the advanced stage include:

a) Chronic arthritis
b) Tophi
c) Bone and joint destruction visible on a radiograph
d) All of the above

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3.	a	b	c	d
4.	a	b	c	d
5.	a	b	c	d
6.	a	b	c	d
7.	a	b	c	d
8.	a	b	c	d

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