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Renewed Approaches to Early Diagnosis of Gout

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Abstract: *Gout is a common inflammatory joint disease associated with the accumulation of monosodium urate crystals. Early diagnosis plays a key role in preventing complications, but traditional methods may not be accurate enough. The article assessed modern methods of gout diagnostics, including ultrasound (US), computed tomography (CT) and polarization microscopy, in terms of their sensitivity and specificity. Data of patients with suspected gout were analyzed. Various diagnostic methods were used, including clinical examination, laboratory tests and imaging technologies (X-ray, ultrasound, CT, MRI). Ultrasound revealed urate deposits in most patients with gout, confirming its value for early diagnosis. Polarization microscopy showed the presence of sodium urate crystals in the synovial fluid of patients with gout. CT and MRI demonstrated high accuracy in detecting tophi and bone erosions. An integrated approach to gout diagnostics, including ultrasound, microscopy and other modern methods, increases the accuracy of disease detection and facilitates timely initiation of therapy.*

Keywords: *gout, diagnostics, ultrasound, computed tomography, polarization microscopy, magnetic resonance imaging.*

Gout is a systemic tophaceous disease characterized by the deposition of monosodium urate crystals in various tissues and the resulting inflammation in individuals with hyperuricemia caused by environmental and/or genetic factors. Gout is the most common inflammatory joint disease in the adult population, leading to a decrease in the ability to work of young and middle-aged people and associated with a deterioration in the quality of life [1]. In addition, gout can be a cause of the development of cardiovascular diseases. Moreover, the latter are the main cause of death in patients with gout. Thus, a study that included 61,527 people noted a link between gout and a high risk of overall and cardiovascular mortality [2].

According to population studies, the prevalence of gout ranges from 1 to 4% [3]. Thus, in the USA, the prevalence of gout reaches 3.9% of the adult population (8.3 million people) [4]. Modern epidemiological studies indicate an increase in the prevalence of gout in the world in recent decades, which is associated with changes in diet, lifestyle, and an increase in life expectancy [6]. In the study of Kuo C. et al. [5] It was noted that the prevalence of gout in the UK in 2012 was 2.49%, and the number of newly diagnosed cases was 1.77 per 1000 population, which was 63.9 and 29.6% higher than the 1997 data. According to Lu X. et al. [6], the prevalence of gout and hyperuricemia in a cohort of elderly people in Beijing was 2.8 and 18.1%, respectively. Once known as the “disease of kings”, this pathology is increasing not only in countries with a high standard of living, but also in regions where gout was previously considered a rare disease [7].

Traditionally, gout is considered to be predominantly found among men over 45 years of age. However, the current trend is a decrease in the age of onset of the disease and an increase in gout cases among women. The NHANES study [8] demonstrated that the prevalence of gout in women in the USA increased to 2%, and amounted to 2.2 million. It was noted that the onset of gouty arthritis in women is on average 10 years later than in men [9]. Among the possible causes of sexual dimorphism is the influence of estrogens, which have a pronounced uricosuric effect; after the onset of menopause, this effect is lost [10]. A number of studies have noted that in most women, the onset of gout is observed in the postmenopausal period. At the same time, gender differences in the incidence of gout are practically leveled out in old and senile age [11]. An obligatory risk factor for the development of gout is persistent hyperuricemia, i.e. an increase in the concentration of uric acid in the blood serum [12]. Uric acid is the end product of purine (urate) metabolism, which is formed as a result of the enzymatic oxidation of xanthine under the action of xanthine oxidase. In the human body, more than 98% of uric acid is converted into monosodium urate, the content of which determines the concentration of uric acid. The overall urate balance of the body can be disturbed as a result of either increased intake or synthesis of purines with subsequent increased renal excretion of urates and their secondary retention in the event of insufficiency of this renal function, or primary damage to those renal functions that cause the excretion of urates [13]. Hyperuricemia is considered to be the content of uric acid in the blood serum> 360 μmol / l (6 mg / dl) [14]. If gout is suspected, the patient examination scheme includes:

- physical examination, including assessment of joint status, blood pressure measurement;
- anthropometric measurements (height, body weight, waist and hip circumference, their ratio);
- social history (diet and lifestyle characteristics);
- identification of a family predisposition to gouty arthritis, arterial hypertension, obesity, diabetes mellitus, coronary heart disease;
- determination of biochemical parameters: blood uric acid levels, urea, creatinine, glomerular filtration rate, fasting blood glucose, aspartate aminotransferase, alanine

aminotransferase, bilirubin, lipid profile study (total cholesterol, triglycerides, high-density lipoprotein cholesterol);

- ECG, echocardiography.

The glomerular filtration rate is one of the main indicators that is taken into account both when choosing anti-inflammatory therapy and monitoring antihyperuricemic therapy.

The "gold standard" of gout diagnostics is the detection of sodium monourate crystals by polarization microscopy. According to the recommendations of the European League Against Rheumatism (EULAR, 2006), a definite diagnosis of gout is made when sodium monourate crystals are detected in the synovial fluid [15]. That is why, if gout is suspected at the time of arthritis, it is necessary to perform a puncture of the affected joint with an examination of the synovial fluid using light or polarization microscopy [16]. Moreover, sodium monourate crystals are determined in the synovial fluid and are also detected in the interictal period.

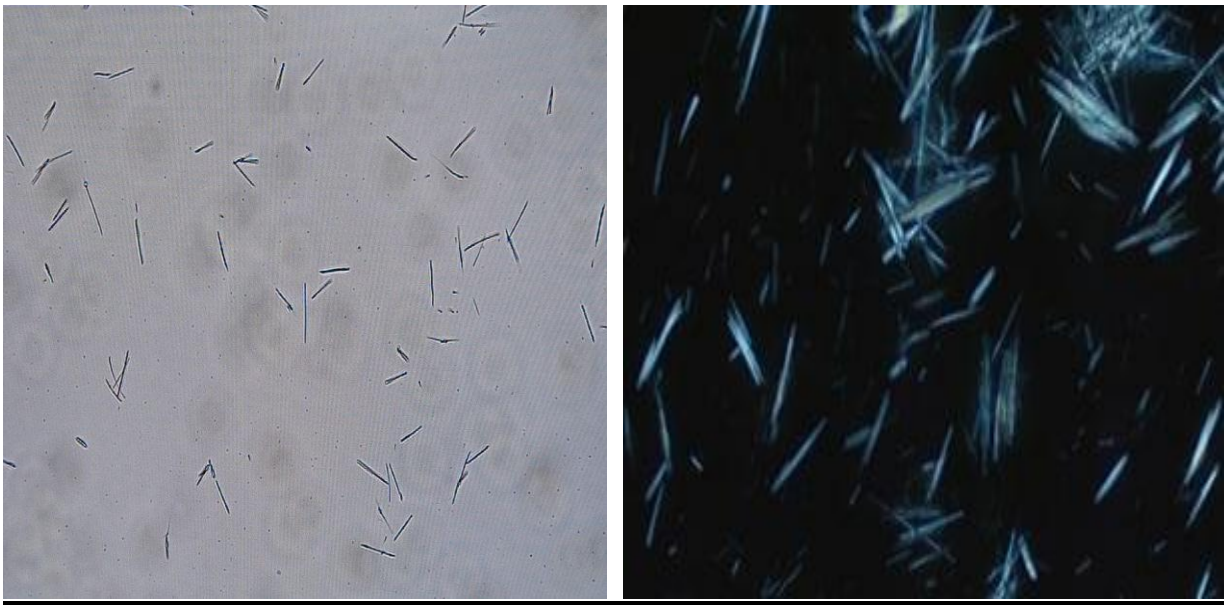


Fig. 1. Monosodium urate crystals from tophus aspirate.

It should be emphasized that the concentration of uric acid in the blood serum is not an indicator that excludes or confirms gout [17]. Moreover, during an attack of gout, the content of uric acid in the blood serum can decrease [18], so this study should be carried out some time after the resolution of arthritis.

Ultrasound examination of joints (US) allows detecting urate deposits in soft tissues, joints, cartilage, as well as determining bone erosions, the presence of synovitis and increased vascularization. Ultrasound is a widespread, safe, non-contrast agent-requiring and affordable diagnostic method in our country.

It is noted that ultrasound can potentially be used to diagnose gout and evaluate the therapy being administered [19]. Thus, with the help of ultrasound it is possible to determine the deposition of sodium monourate on the surface of hyaline cartilage in the form of an additional light line located parallel to the line of transition of the subchondral bone into cartilage and is called the symptom of the "double contour" [20]. It is determined in acute gouty arthritis, in patients with a history of gout attacks and asymptomatic hyperuricemia. The sensitivity of the sign in gout varies from 25 to 95% [21]. It is assumed that this sign can be considered as an early manifestation of the disease before the development of erosions. However, further studies are needed to determine its sensitivity and specificity as a symptom of early diagnosis of gout and its prognostic value in asymptomatic hyperuricemia.

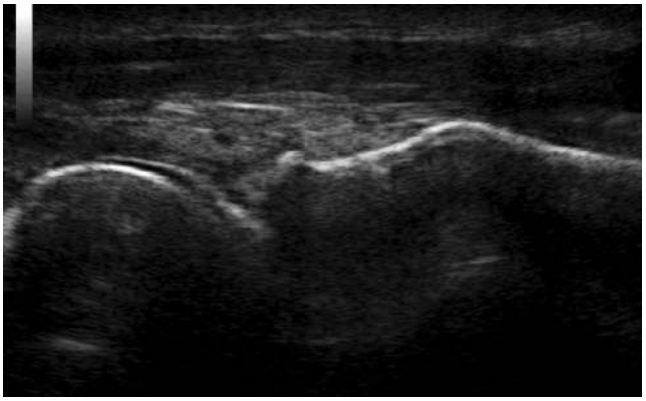


Fig. 2. Linear hyperechoic inclusion of a linear shape in the hyaline cartilage along the contour of the articular surface of the head of the metatarsal bone

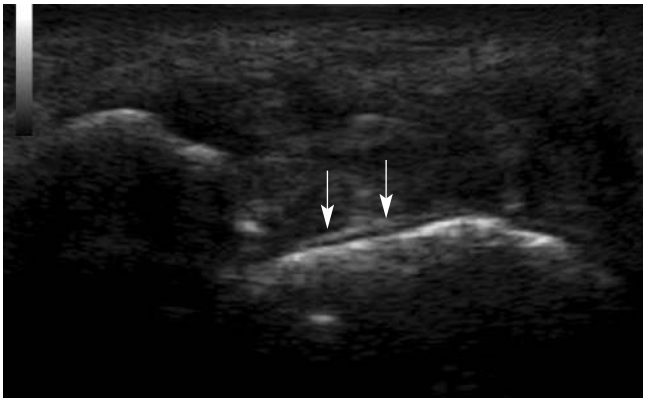


Fig. 3. Thickening of the synovial membrane and a linear hyperechoic inclusion in the hyaline cartilage of the ankle joint of a patient with gout

Ultrasound in gout also allows visualization of tophi. Determination of tophi structures facilitates early therapeutic measures. In addition, ultrasound is a more sensitive method than radiography for diagnostics of marginal bone erosions, however, underestimation of the size and number of erosions is possible, compared with magnetic resonance imaging (MRI). The specificity of ultrasound diagnostics of erosions increases in the presence of synovitis or tophi. At the same time, if septic arthritis is suspected in patients with microcrystalline arthritis, EULAR recommends Gram staining and synovial fluid culture [11]. Computed tomography (CT) allows identification of urate crystal aggregates and differential diagnosis with other diseases. The method is highly accurate in detecting tophi located both intraosseously and in the area of tendons and soft tissues; it is highly sensitive in determining the volume of urate crystals [6]. At the same time, further studies are needed to determine the sensitivity and specificity of CT in detecting the earliest stage of gout before the formation of crystal aggregates (crystals smaller than 3 mm, microtophi, crystal deposits on cartilage, etc.) [22]. CT can be useful in diagnosing patients with a high probability of tophaceous gout based on clinical data, when conventional diagnostic tests are inconclusive. Moreover, the method is of particular importance in cases of atypical gout localization (e.g., tophaceous lesions of the spine). Computed tomography is a highly sensitive method for visualizing erosions and tophi characteristic of gout. However, the routine use of CT is limited by its high cost and radiation exposure.

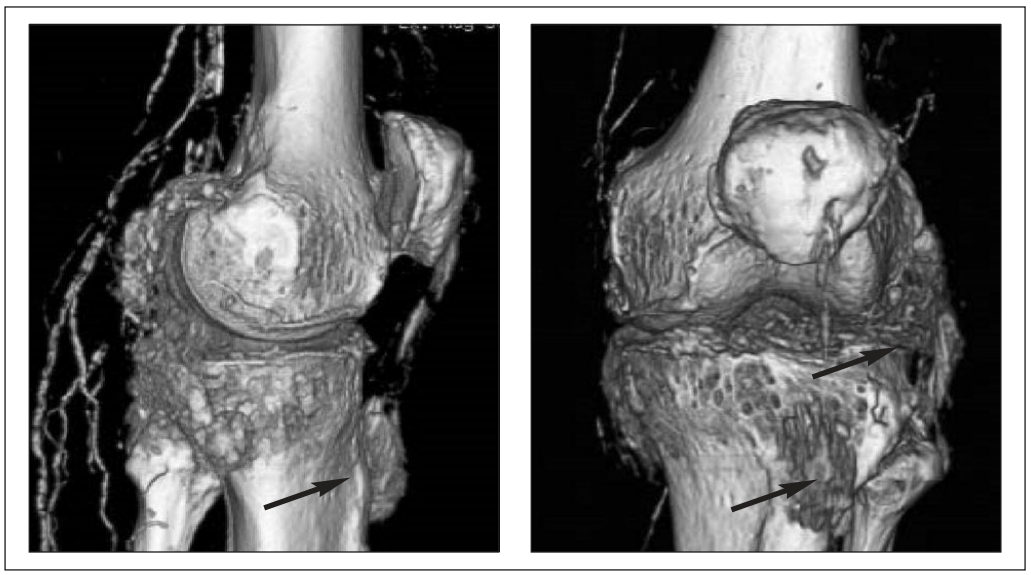


Fig. 4. CT of the knee joints. Multiple tophi in the soft tissue area (arrows)

Magnetic resonance imaging allows visualization of the location, size, structure of tophi, changes in articular cartilage, synovial membranes, joint bags that are not determined by radiography [6]. It has been demonstrated that MRI is superior to standard radiography in identifying tophi. It has been established that the sensitivity of MRI is 93.9%, specificity is 80%, while with radiography - 80.6 and 66.7%, respectively [2]. There are reports of the development of tophi at the onset of gout, up to the manifestation of classic signs of arthritis [3], however, there are certain difficulties in interpreting the MRI results, since the image of tophi is variable. MRI with gadolinium is recommended for differential diagnosis with osteomyelitis.

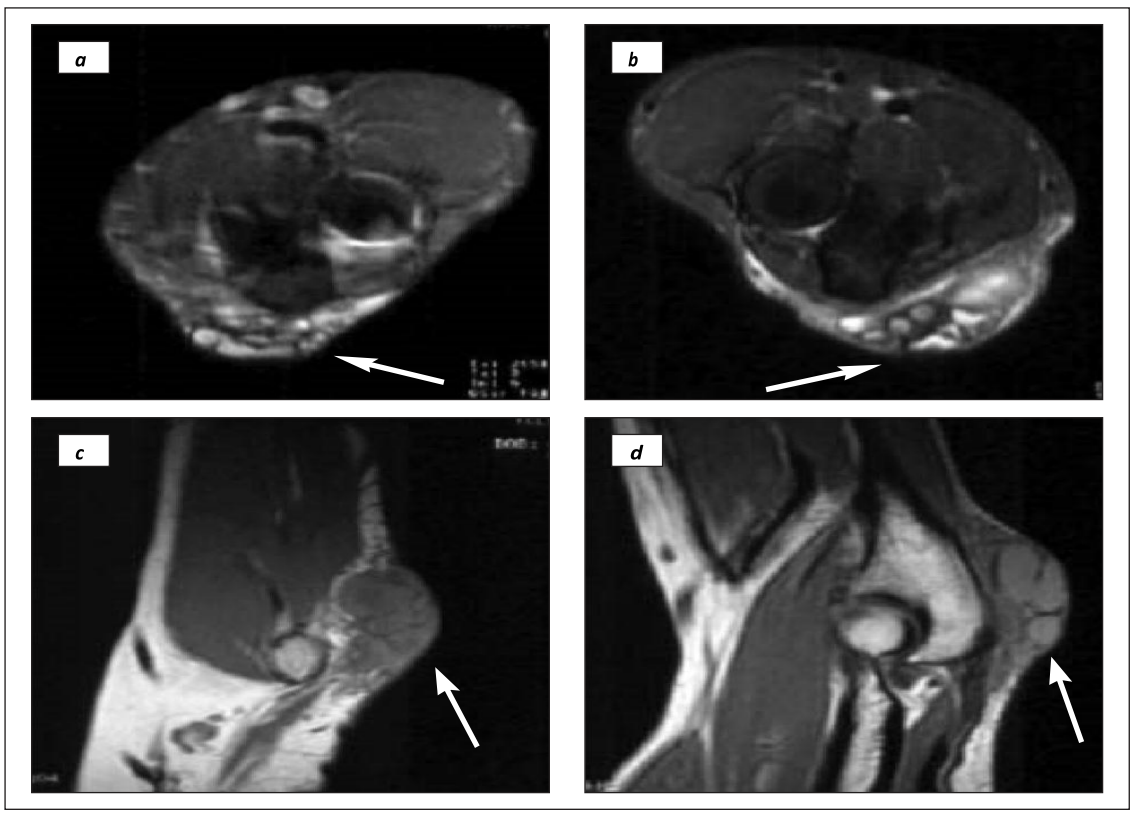


Fig. 5. MRI of the left elbow joint. a, b – STIR mode, transverse sections; c, d – SET1 mode,

sagittal sections.

In the area of the olecranon there is a soft tissue formation – tophus (shown by white arrows) with clear boundaries and septal septa without signs of perifocal soft tissue edema. The musculoskeletal system is unchanged.

Table 1 presents a comparative assessment of the diagnostic significance of visualization methods.

Table 1.

Significance of additional methods in the diagnosis of gout

	Ro	Ultrasound	CT	MRI
Erosions	+	++	+++	++
Effusion	+	+++	++	+++
Proliferation of synovium	-	+++	+	+++
Tophi	+	+++	++	+++
Narrowing of the joint space	+++	-	+++	+++
Tendon pathology	-	+++	++	+++
Bone marrow edema	-	-	+	+++
Tophi or synovial vascularization	-	+++	-	+++

Notes: CT – computed tomography; MRI – magnetic resonance imaging; US – ultrasound examination; Ro – radiographic examination;

Within the framework of the 3rd initiative (Evidence, Expertise, Exchange), the most frequently encountered questions (Table 2) arising in the process of diagnosis and treatment of patients with gout were summarized and the answers were presented [5]. Each item was assessed according to the level of evidence, for each item the average level of agreement was calculated on a 10-point scale, where 10 points corresponded to complete agreement with the final wording.

Table 2.

Clinical questions within the framework of the 3rd initiative (Evidence, Expertise, Exchange)

1. When can gout be diagnosed clinically, with or without laboratory tests or imaging, and when is crystal identification necessary?
2. Should we routinely screen patients with hyperuricemia and/or a diagnosis of gout for comorbidities and cardiovascular risk factors?
3. What is the role of glucocorticoids, colchicine and nonsteroidal anti-inflammatory drugs, interleukin-1 inhibitors, and paracetamol in the treatment of acute gout?
4. What lifestyle interventions (such as diet, alcohol restriction, weight loss, smoking cessation, and/or exercise) are effective in the treatment and prevention of gout?
5. What are the efficacy, cost-effectiveness, and safety of urate-lowering agents (allopurinol, febuxostat, peguricase, benzbromarone, and probenecid) in the treatment of gout? What sequence or combination of urate-lowering agents should be recommended?
6. What is the best treatment for preventing an acute attack while on urate-lowering therapy, and for how long should it be given? What is the optimal time to start urate-lowering therapy after an acute attack of gout?
7. How do comorbidities (e.g., metabolic syndrome, cardiovascular disease, gastrointestinal

disease, and renal disease) influence the choice of specific agents (particularly colchicine, allopurinol, and other urate-lowering agents) in gout for an acute attack of arthritis, chronic gout, and for the prevention of an acute attack of arthritis?
8. What should be the goal of treatment and how should patients with gout be followed over time (e.g., patient-reported disease course, clinical, biochemical, and/or imaging data)?
9. How should tophi be managed?
10. Can we prevent gouty arthritis, renal damage, and cardiovascular events by lowering serum uric acid levels in patients with asymptomatic hyperuricemia? If so, what should the target levels be?

In 2014, international guidelines for the treatment and diagnosis of gout were published (Table 3) [4].

Table 3.

International guidelines for the treatment and diagnosis of gout

Recommendation	Level of evidence	Level of confidence	Level of agreement
1. Crystal identification should be performed to establish a definite diagnosis of gout; if this is not possible, the diagnosis of gout can be confirmed by the presence of classic clinical features* (such as acute arthritis of the first metatarsophalangeal joint, tophi, rapid response to colchicine) and/or detection of characteristic imaging features**.	*2b **2b	*D **B	8,8 (SD 1,6)
2. In patients with gout and/or hyperuricemia, renal function should be determined and assessment of cardiovascular risk factors is recommended.	2c	C	8,4 (SD 2,1)
3. In acute gout attacks, low-dose colchicine* (up to 2 mg daily), NSAIDs** and/or glucocorticoids (intra-articular***, oral**** or intramuscular***** depending on comorbidities and risk of adverse reactions) should be administered.	*1b **1a ***4 ****1a *****1a	*D **D ***D ****D *****D	8,9 (SD 2,1)
4. Patients should be advised to adopt a healthy lifestyle, including losing excess weight, exercising regularly, stopping smoking, and avoiding excessive alcohol and sugar-sweetened beverages.	5	D	8,5 (SD 1,7)
5. Allopurinol should be the first-line urate-lowering therapy*; uricosurics** (e.g., benzbromarone, probenecid) or febuxostat*** may be used as alternatives; uricase as monotherapy should be considered only in patients with severe gout in whom all other forms of therapy are ineffective or contraindicated****. Urate-lowering therapy (in particular, uricase) should be initiated at low doses and titrated to achieve target serum uric acid levels*****	*2b **2b ***2b ****2b *****5	*C **C ***C ****C *****D	9,1 (SD 1,3)
6. When urate-lowering therapy is prescribed, the patient should be informed of the possible risk of arthritis flares and their treatment*. Prophylaxis should be with colchicine (up to 1.2	*5 **1b ***5	*D **B ***D	8,1 (SD 2,1)

mg/day)**, and if contraindicated or poorly tolerated, NSAIDs*** or low doses of glucocorticoids**** may be used. Duration of prophylaxis depends on the individual patient characteristics.	****5	****D	
7. In patients with mild to moderate renal impairment, allopurinol may be used with careful monitoring for adverse reactions, starting with a low dose (50–100 mg) and titrating to target serum UA levels*. Febuxostat** and benzbromarone*** are alternative agents that can be used without dose adjustment.	* 4 **2b ***4	* D **B ***D	8,5 (SD 1,7)
8. The goal of treatment is serum UA levels below 0.36 mmol/L (6 mg/dL) and, ultimately, the absence of gouty arthritis attacks and resolution of tophi*; monitoring should include monitoring serum UA levels, frequency of arthritis attacks, and tophi size**.	* 2b ** 1 b	* C ** B	9,0 (SD 1,8)
9. To eliminate tophi, it is necessary to ensure a stable serum uric acid concentration, preferably below 0.30 mmol/L (5 mg/dL); surgical treatment is required only in individual cases (e.g., compression of nerves or other soft tissues, as well as the development of infection).	2b	B	9,2 (SD 1,4)
10. Pharmacological treatment of asymptomatic hyperuricemia for the prevention of gout, kidney disease, or cardiovascular events is not recommended.	2b	D	8.6 (SD 2.5)

Abbreviations: UA – uric acid; NSAIDs – non-steroidal anti-inflammatory drugs;

Conclusion Thus, the diagnosis of gout is not as simple as previously thought. It should be especially emphasized that late diagnosis of gout is explained by several factors. This includes insufficient knowledge of the diagnosis and treatment of gout among primary care physicians [7]. However, it is impossible not to note the late appeal of patients to the doctor and long-term self-medication (the presented clinical case). In addition, low compliance of patients, who often neglect the advice and recommendations of doctors [22] leads to frequent exacerbations of gout, protracted course of exacerbations and long-term disability. The use of accepted modern diagnostic algorithms in clinical practice improves the diagnosis of gout and, most importantly, in the early stages, as well as implement modern treatment strategies aimed at improving the quality of life of patients and the prognosis of the disease in general, as well as reducing treatment costs.

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