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THE ROLE OF ULTRASOUND IN DETECTING URATE DEPOSITS

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Abstract

The rising prevalence of hyperuricemia, influenced by changes in diet, underscores the importance of conducting population-based epidemiological research, especially in regions lacking sufficient data. In addition to the well-documented complications of hyperuricemia on renal and articular aspects, elevated serum uric acid levels are identified as a significant risk factor for cardiovascular diseases, strokes, joint manifestations, and renal failure. Prolonged asymptomatic hyperuricemia may lead to vascular and articular lesions. This condition is characterized by an increase in plasma uric acid levels without clinical signs of gout, posing a therapeutic challenge due to uncertainties surrounding the risk-benefit ratio of urate-lowering treatments [ULTs]. While the need to treat asymptomatic hyperuricemia is still a topic of debate, the detection of urate deposits through imaging, particularly osteoarticular ultrasound, emerges as a crucial indicator. Various imaging techniques, such as synovial fluid microscopy, computed tomography [CT], dual-energy computed tomography [DECT], and osteoarticular ultrasound, assist in identifying uric acid crystal deposits, with DECT being an innovative method. Osteoarticular ultrasound provides a unique opportunity to better characterize individuals with hyperuricemia and gout, influencing the determination of therapeutic goals and clinical directions. Specific signs like "double contour" and tophi, assessed by color Doppler, contribute to diagnostic precision. Osteoarticular ultrasound serves as a potentially significant tool for diagnosing, assessing, and monitoring gout pathology, offering the possibility to decide on and evaluate treatment effectiveness. Despite its utility, the reproducibility of osteoarticular ultrasound requires thorough investigation. This tool proves crucial in the nuanced management of asymptomatic hyperuricemia, providing valuable insights into the patterns of urate crystal deposition and guiding therapeutic interventions.

Keywords: Gout, Ultrasound, Hyperuricemia, Hidden Gout, Urate Deposits.

1. BACKGROUND

While the necessity of treating asymptomatic hyperuricemia [AH] is subject to debate, the identification of urate deposits [UDs] through imaging methods, particularly osteoarticular ultrasound [OAUS], is emerging as a significant indicator [1]. The therapeutic management of AH poses challenges due to the uncertainty surrounding the risk-benefit ratio of urate-lowering treatments [ULTs] [2].

This frequent biological observation results from an excess production of uric acid and/or a impairment in its renal elimination. Uric acid [UA], with its antioxidative, pro-oxidative, and pro-inflammatory properties, can negatively impact various organs [3]. Research indicates its associations with renal and vascular lesions, hypertension, and oxidative stress in blood vessels [4, 5]. Over the past two decades, there has been a growing

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prevalence of comorbidities associated with hyperuricemia [6], with the clinical emergence of gout when hyperuricemia persists [5, 6].

In this context, the use of ultrasound to detect UDs appears crucial. Studies suggest a frequency of UDs in AH ranging from 32 to 42% [7], with ultrasound standing out as a simple and cost-effective method to identify these deposits [8]. However, clear recommendations for the management of this population at risk of developing gout are yet to be formulated [9].

2. OVERVIEW OF HYPERURICEMIA

The increasing prevalence of hyperuricemia, especially in industrialized countries, reflects a dietary shift promoting the consumption of purines, primarily found in sugary and alcoholic beverages. Although this trend is global, regional variations persist, as evidenced by estimated rates between 20 and 25% in the United States, with a higher incidence among African Americans [10, 11]. In Japan, the prevalence is approximately 30%, with a significant increase over a decade, especially in individuals over 65 years old [12].

Systematic literature reviews reveal prevalence data for hyperuricemia in 24 countries, highlighting a more pronounced frequency in Asia and notable variations, ranging from 1% in Papua New Guinea to 85% in the Marshall Islands [12]. In New Zealand, gout is on the rise, linked to an interplay of genetics, environment, and dietary habits, particularly impacting the Maori population [12, 13].

While hyperuricemia is more predominant in men, only 5% of gout patients are women, a proportion that decreases after menopause [14]. In children, the threshold for normal UA levels is lower than in adults, with a tendency for increased hyperuricemia with age [14]. Hypertension is frequently associated with an elevated UA level, correlating with increased morbidity [10,15].

The growing burden of gout, coupled with obesity and global aging, underscores the imperative to develop prevention and management strategies for hyperuricemia. Encouraging population-based epidemiological research, especially in data-deficient regions, becomes an urgent necessity [16].

3. CONSEQUENCES OF HYPERURICEMIA

In addition to the well-documented complications of hyperuricemia on renal and articular levels, elevated levels of serum UA are identified as a major risk factor for ischemic heart diseases, strokes, peripheral artery diseases, and renal failure. This risk persists even after correcting for other factors such as metabolic syndrome and the use of uric acid-inducing diuretics [17-18].

Chronic hyperuricemia triggers the precipitation of UA in joints and tissues, potentially leading to asymptomatic UDs or progressing to gouty arthritis, and even deposits in the urinary tract and chronic nephropathy. This progression depends on various endogenous

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and exogenous factors, with persistently high levels of serum UA exceeding 60 mg/l particularly conducive to prolonged deposits over time. Studies identify predictive factors, including age, body mass index [BMI], hypertension, cholesterol levels, and alcohol consumption [17].

According to defined thresholds, the prevalence of hyperuricemia reaches 15-20%, while UDs are observed in only 4% of cases, mainly in men over 50. Although hyperuricemia is recognized as the primary risk factor for gout, other elements can promote tophi formation. Before the clinical manifestation of gout, AH often precedes the first gouty arthritis attack. The transition to advanced gout varies from person to person, with stages ranging from AH to chronic gouty arthritis, highlighting the complexity of this progression. This can be divided into different stages:

Stage 1: Asymptomatic hyperuricemia

When the serum UA concentration exceeds 68 mg/l, urate salt crystals may begin to deposit, potentially contributing to organ deterioration.

Stages 2 and 3: Acute gout and intercritical periods

UDs around joints, activated by local factors, can trigger gout attacks. These intermittent phases, called "intercritical periods," still exhibit crystal deposits that may serve as a nidus for future attacks.

Stage 4: Advanced gout

If crystal deposits continue to accumulate, patients may develop chronic arthropathies, representing the advanced stage of gout. Therapy can intervene to halt progression and prevent the clinical expression of this advanced stage.

4. TOOLS FOR DETECTING MONOSODIUM URATE CRYSTAL DEPOSITS

4.1. Synovial fluid microscopy:

The search for monosodium urate [MSU] crystals is a crucial step in understanding gout. Although hyperuricemia is a prerequisite for crystallization, not all hyperuricemic individuals develop gout, indicating the complexity of MSU crystal formation [19]. Conversely, some patients in a gout flare may have normal serum UA levels [≤ 60mg/l], emphasizing the delicate relationship between these levels and UA crystallization [20].

Physicochemical factors play a key role in MSU genesis, with local and/or systemic conditions capable of modulating their solubility, precipitation, and stability. A thorough study of synovial fluid from asymptomatic knees of 50 gout patients revealed that 58% had MSU deposits in knee joints. Among patients consenting to aspiration of both knees, 37% had bilateral MSU crystals, and 32% had unilateral crystals [21].

A notable observation was made regarding the first metatarsophalangeal joints of asymptomatic gout patients, where a significant portion had MSU deposits in the synovial fluid of their MTP [22]. Detection of these MSU crystals in joint fluid or even in a tophus,

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in the form of needle-shaped crystals with strong birefringence under polarized light microscopy, remains the predominant diagnostic examination for confirming gout [21].

4.2. Computed tomography:

Computed tomography [CT] serves as a valuable complementary imaging method for evaluating deep structures when methods without ionizing radiation cannot confirm their presence, particularly surpassing radiography in these specific situations [23]. It provides accurate visualization of tophi in subcutaneous tissue and intra-articular areas, surpassing radiography [23]. CT's increased sensitivity also detects bone erosions more effectively than radiography and magnetic resonance imaging [MRI] [23]. According to a systematic analysis, CT identifies intraosseous tophi in 81% of joints with erosion, reaching 100% when erosion exceeds 7.5 mm [24].

CT can also reveal MSU deposits inside tophi, distinguishing their attenuation near 160 HU from that of calcium deposits, which exhibit higher attenuation, around 450 HU [25]. This allows for precise differentiation of nodules in soft tissues. In cases involving deep structures such as the spine, CT can complement an MRI study, highlighting tophi masses with compression of nerve structures [23].

Although CT can prove useful, it is not the preferred method for evaluating gout on surface structures due to significant exposure to ionizing radiation [23].

4.3. Dual Energy Computed Tomography [DECT]:

Dual Energy Computed Tomography [DECT] emerges as an innovative method providing details on the chemical composition of tissues, enabling their distinction. This approach proves capable of differentiating MSU crystals associated with gout from bone or dystrophic calcifications [26]. Studies on joint and periarticular crystal deposits with DECT have revealed high sensitivity and specificity, underscoring its diagnostic precision [27].

However, in the early stages of the disease, when MSU deposits are microscopic, and intra-articular tophi are not macroscopic, DECT may not detect them due to its size threshold, typically set at 2 mm [28]. Despite these limitations, DECT can be used to assess gout independently of serum UA levels, calculating the overall burden of UA deposits on individual lesions, joints, or fully scanned areas [29].

While DECT may have weaknesses, including artifacts related to metallic devices and calluses, it can confirm or exclude the disease in patients with normal or elevated serum UA levels. Its use for treatment monitoring remains primarily limited to clinical trials of new therapeutic agents due to its cost and radiation exposure, although the latter remains below the annual natural dose received and well below carcinogenic thresholds [23].

4.4. Osteoarticular ultrasound:

Osteoarticular ultrasound exploration provides a unique opportunity to better characterize individuals with hyperuricemia and gout, thereby influencing the determination of therapeutic goals and clinical approaches. The frequent detection of monosodium urate

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[MSU] crystal deposits via ultrasound in patients with AH suggests a potential redefinition as "asymptomatic gout." This observation sparks discussion on the necessity of treating these patients to eliminate UDs [30]. In this context, ultrasound proves relevant, especially in cases of chronic hyperuricemia, for all patients, including those with moderate hyperuricemia [≥ 80 mg/l] over an extended period [e.g., ≥ 2 years], due to its rapid execution [less than 10 minutes] [31].

In individuals with gout without visible tophi, ultrasound has allowed the detection of subclinical UDs and tophi in half of the patients, thereby expanding the clinical definition of "tophaceous gout" [30]. Surveys on asymptomatic subjects with a family history of gout have also revealed significant prevalences of hyperuricemia with MSU deposits, even in those with moderate serum UA levels starting from 50 mg/l [32].

A study involving patients with AH for at least two years revealed the presence of UDs [tophi] in tendons, synovium, and other soft tissues in 34% of participants, emphasizing the variability of locations and higher prevalence in knees compared to ankles. Increased vascularity in these areas indicated pathological changes [33].

Although European and American recommendations generally do not advocate treatment for AH [31], some scholarly societies consider initiating urate-lowering therapy based on specific serum UA thresholds, regardless of previous gout attacks. However, this approach requires thorough investigation of its benefits through clinical trials [31].

4.4.1. Specific signs of urate deposits:

- **Double contour sign:**

The "double contour sign" [Fig. 1] serves as a distinctive marker of UDs, manifested by an irregular hyperechoic linear image along the hyaline cartilage border, parallel to the subchondral bone, and lacking a posterior acoustic shadow. It differs from the cartilage interface sign, persisting even after reducing the overall gain and remaining linked to the cartilage during dynamic maneuvers [23]. The prevalence of this sign in the knees of individuals with gout ranges between 25 and 40% [34]. Investigations have also revealed the presence of the "double contour" in the knees of asymptomatic gout patients [34]. In a 2007 study by Thiele, this sign was observed in 92% of patients with biopsy-confirmed gout, and its absence was confirmed in the entire control group.

Individuals with AH may also exhibit the "double contour," identified in Pineda's study in 25% of metatarsophalangeal joints [23]. It is noteworthy that this sign tends to disappear after a mean reduction in UA levels over approximately 7 months [23].

In addition to its diagnostic role, the "double contour" provides added value in monitoring gout patients, showing improvement as early as the third month under ULTs [35].

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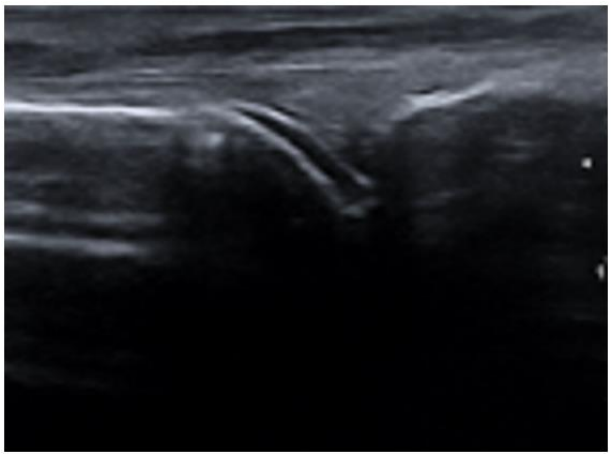

Figure 1: Ultrasound view of a double contour sign on a dorsal scan of a metatarsophalangeal joint

- **Tophus:**

Perez-Ruiz demonstrated that ultrasound has the capability to identify all periarticular tophi identified by MRI. Following these studies, the OMERACT group recognized OAUS as a potentially valuable method for locating and measuring tophi in gout [23]. Understanding the ultrasound characteristics of tophi [Fig. 2] is crucial to differentiate tophaceous nodules from those resulting from other etiologies. OAUS employs criteria to distinguish various nodules arising from malignant, inflammatory, and infectious processes. A 2003 study by Nalbant, comparing tophaceous nodules to rheumatoid nodules, revealed that 80% of tophi were heterogeneous, and 75% were hyperechoic. In contrast, the author observed only 15% heterogeneity and hyperechogenicity in rheumatoid nodules. Rheumatoid nodules are more homogeneous and may present a well-defined hypoechoic central area due to the presence of necrosis. Unlike tophi, rheumatoid nodules rarely calcify, a characteristic that also helps differentiate them from these formations, which may undergo calcification [23]. The detection of tophi on the ultrasound of the first metatarsophalangeal joint [MTP] in gout patients has been reported with a prevalence ranging from 18 to 35% [34]. In contrast, intratendinous tophi, less frequently observed, seem to evolve towards tendon rupture [23]. An early diagnosis by ultrasound can guide the physician toward effective treatment, preventing injuries that, without medical intervention, could require surgical intervention. Within tendons, tophi may exhibit microdeposits revealed by ovoid hyperechoic spots. The hyperechogenicity observed in tophi corresponds to UDs or calcifications. Chronic intratendinous tophi can be identified by hyperechoic bands, sometimes accompanied by a posterior acoustic shadow. Small hyperechoic particles, also called bright spots, measuring less than 1 mm, represent microtophi in the synovium. The clustering of microtophi forms the hyperechoic tophus; thus, hyperechogenicity and heterogeneity serve as powerful indicators of the tophus. The hypoechoic halo around the tophus is a hypoechoic band partially or entirely observed around the tophus, which may correspond to inflammation, fibrosis, or edema.

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This halo is frequently observed in large portions of tophi and may serve as a marker of the tophaceous nodule. The dimensions of the gouty tophus are crucial in assessing the response to treatment. Therefore, for practical utility, the method used for this purpose must demonstrate good reproducibility.

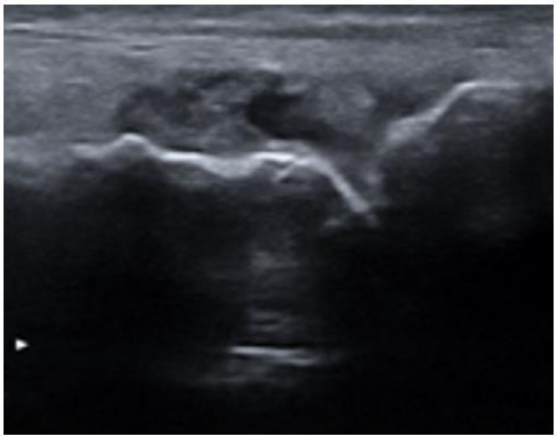

Figure 2: Ultrasound view of numerous tophi on a dorsal scan of a metatarsophalangeal joint

- **Aggregates:**

These are clusters of intra-synovial debris that may provide a favorable environment for the subsequent emergence of tophi. They are hyperechoic and heterogeneous foci that maintain a high degree of reflectivity, even when the gain setting is minimized or the probe angle is modified. Moreover, these foci may occasionally generate a posterior acoustic shadow.

- **Snowstorm:**

Typically observed during gout attacks, they are unlikely in cases of AH. These images are characterized by heterogeneous hyperechoic areas in the synovium, with or without Doppler signals. Their prevalence reaches nearly 90% in gouty arthritis, especially at the metatarsophalangeal joint of the big toe [36].

4.4.2. Non-specific signs:

- **Intra-articular effusion and synovitis:**

OAUS provides visualization of changes in the inflammatory process associated with gout. Color Doppler assessment reveals an increase in blood flow during the acute phase of gouty flare, partially normalizing within 7 days [23]. Outside of gout flare, color Doppler usually does not show flow, although atypical cases of gouty arthralgia may present hyperechoic tophi and Doppler flow, even in the absence of classic flare signs. A study revealed that 34 to 42% of patients with AH had clinically asymptomatic UDs [microtophi], with 24% showing signs of inflammation on ultrasound [31]. The presence of UDs in asymptomatic patients was associated with an increased degree of coronary calcification,

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suggesting a possible influence of crystal deposit-mediated inflammation, although this explanation remains to be confirmed [31].

- **Tenosynovitis:**

Enthesopathy secondary to UDs is a recent discovery, although its prevalence accounts for only 7% of cases of chronic tophaceous gout. However, this possibility should be considered in the differential diagnosis, considering the clinical context. The ultrasound characteristics of tophi compared to tendons can help understand clinical pictures showing movement restrictions in patients with chronic tophaceous gout and avoid invasive procedures such as biopsies. A classification into five types of the relationship between tophi and tendons has been proposed, based on their location [23].

- **Cortical Erosion:**

Bone erosions, defined as cortical discontinuities in two perpendicular planes, are a late manifestation with low sensitivity for diagnosing tophaceous gout. OAUS shows slightly better detection than radiography [24% versus 20% of cases]. A comparative study among participants with gout, AH, and a control group showed a higher prevalence of bone erosions and synovitis in the first two groups, with larger tophus dimensions and erosions [37].

4.4.3. Sensitivity and specificity of osteoarticular ultrasound [OAUS]:

OAUS presents a potentially significant tool for the diagnosis, assessment, and monitoring of gout pathology, offering the ability to make treatment decisions and evaluate effectiveness. Despite its utility, the reproducibility of OAUS in evaluating gouty arthropathy requires thorough study [31]. OAUS identifies different chronological presentations of gout pathology, determining the extent of tissue damage early and non-invasively, with low variability among observers or operators [23].

The likelihood of AH progressing to gout is proportional to serum UA concentrations and the duration of evolution. A UA level ≥ 100 mg/l increases the risk of developing gout within 5 years in approximately 50% of patients [31].

A study conducted in 2008 by Rettenbacher demonstrated a sensitivity of 80% and specificity of 75% for bright hyperechoic foci in synovial tissue [microtophi = snowstorm] and 79% and 95% for the double contour sign in diagnosing gout pathology [23]. When these two findings are combined, specificity reaches 100%, but with a significant reduction in sensitivity [23]. Considering either of these findings, ultrasound exhibits a sensitivity of 96% and specificity of 73%. However, specificity is not maximized, as punctate hyperechoic foci can also be observed in other conditions such as osteoarthritis, rheumatoid arthritis, and chondrocalcinosis [23]. A study on 824 gout patients showed a sensitivity of 76.9%, specificity of 84.3%, positive predictive value [PPV] of 83.3%, and negative predictive value [NPV] of 78.1% for the presence of UDs. Sensitivity was higher in subjects with a disease duration of at least 2 years and those with subcutaneous nodules on examination [presumed tophus] [38].

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Comparatively, some studies have revealed that ultrasound is more sensitive than radiography and allows for earlier detection of lesions, making it particularly valuable in monitoring gouty arthropathy [23].

5. FACTORS EXPOSING TO URATE DEPOSITS

Comparing AH groups with and without deposits, a significant male predominance is observed in subjects with UDs, most often aged over 50 and with a BMI exceeding 30 kg/m² [39]. A Korean study on subjects with AH [40] revealed that BMI in the group with UDs was higher than in the group without UDs, approaching 28 kg/m². This study suggests obesity as a risk factor for UDs in AH.

The question also arises whether prolonged exposure to high blood UA levels would expose to joint and periarticular UDs. Elevated UA levels appear to be a key risk factor for the development of UDs. A study involving nearly 19,000 participants without gout showed an increasing incidence of gout depending on serum UA concentrations, ranging from 0.33% to 26% for initial levels: <60 mg/l and ≥100 mg/l, and rising at 5 years to 1.1% and 49% at 15 years, respectively [41]. These results suggest that prolonged exposure to high UA levels is a risk factor for UDs. Genomic studies have identified several new common genetic factors associated with hyperuricemia and gout, especially those involved in renal UA transport, such as renal transporters SCL22A12, SCL2A9, and GLUT9 [42]. A study examining OAUS-documented UMS microcrystals in synovial fluid from subjects with a family history of gout revealed a high proportion of these crystals, even with uricemia between 50 and 70 mg/l, reinforcing the hypothesis of genetic involvement [43]. Over half of the subjects with UDs have UA levels above 80 mg/l.

In an Algerian study evaluating the presence of UDs through OAUS in a population with AH, variables significantly influencing UDs are UA levels, male gender, and BMI, based on their p-values [<0.05]. For women, significant variables, according to their p-values [<0.05], are UA levels and diuretic intake. No significant link is observed between diuretic intake and male gender [p-value of 0.1048]. Thus, the risk of UDs was 4.73 times higher in women taking diuretics compared to those not taking them. Most women were postmenopausal due to their advanced age in the sample, and menopause did not show a significant link to the risk of UDs [p-value = 0.4037]. This analysis demonstrates that diuretic intake in women with AH is a notable risk factor for UDs. These results correspond to those of Wafaa Gaber's study, which observed a higher frequency of the double contour in OAUS in patients taking diuretics, especially when uricemia exceeds 90 mg/l [44]. A study on diuretic-induced gout, including 426 participants, suggests that genetic factors play a less important role in this form of gout compared to primary gout. Clinical and genetic characteristics of gout associated with diuretics were analyzed using a case-control study design [diuretic group versus non-diuretic group]. In the group taking diuretics, there were more women, higher rates of comorbidities, higher BMI, higher serum urate levels, and lower estimated glomerular filtration rate compared to those not taking diuretics. The risk allele ABCG2 rs2231142 was less frequent in the diuretic group

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[36.1%] compared to those without diuretics [47.6%, p = 0.00012] [45]. Understanding the link between diuretic intake and the risk of gout, especially in women, remains complex and requires in-depth research.

Various studies on UDs in AH have limitations, including the heterogeneity of ultrasound devices, inconsistency in hyperuricemia definitions, low methodological quality, clinical or demographic heterogeneity, inconsistencies in reports, potential underestimation of lesion prevalence in rare sites, exclusive use of OMERACT definitions, and the lack of assessment of effusion and synovitis. These limitations can introduce recruitment and interpretation biases.

6. CONCLUSION

Ultrasound emerges as a leading diagnostic tool, offering appreciable sensitivity in detecting UDs, especially through the identification of bright hyperechoic foci in synovial tissue and the double contour sign. This imaging modality proves to be a promising ally for the chronological assessment of joint manifestations of gout, with demonstrated ability to detect tissue lesions early and guide therapeutic decisions.

The analysis of exposing factors underscores the impact of BMI, age, and serum UA levels in the development of UDs, reinforcing the need for a multifactorial approach in assessing hyperuricemia. Genetic investigations confirm the predominant role of certain polymorphisms associated with renal UA transport, expanding our understanding of the underlying mechanisms of UDs in the context of AH.

However, despite its advantages, OAUS presents challenges, particularly related to the variability of ultrasound devices and methodological limitations in existing studies. These aspects highlight the need for rigorous standardization and in-depth studies on the reproducibility of this modality in the context of gouty arthropathy.

Conflicts of interest

The authors declare no conflicts of interest.

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