Review

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Musculoskeletal ultrasonography in gout

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Abstract

Gout is a frequent inflammatory disease induced by the deposition of monosodium urate crystals in joints and extra-articular tissues. The natural history of the disease includes four different phases: asymptomatic hyperuricemia, acute attacks, intercritical phase, and chronic tophaceous gout. Imaging techniques have several applications in the diagnosis, clinical monitoring and management of the disease but, particularly, musculoskeletal ultrasound is able to detect a wide set of abnormalities in gout. This review reports the most relevant findings detectable by ultrasound and the current available data in the literature regarding the role of musculoskeletal ultrasound in gout.

Keywords: gout, monosodium urate crystals, ultrasound

Introduction

Gout is an inflammatory disease induced by the deposition of monosodium urate (MSU) crystals in joint and extra-articular tissues [1]. It is the most common form of arthritis in men older than 40 years [2] and its prevalence has increased in the general population in the last decade [3].

Hyperuricaemia, defined as a serum urate level of ≥6.8 mg/dl (6.8 mg/dl represent the limit of urate solubility at physiologic temperature and pH), is a necessary, but not sufficient, condition for the development of the disease [4]. It is due to an overproduction of urate or, more frequently, to reduced renal excretion; the majority (over 80%) of gouty patients have a positive family history of gout or hyperuricemia [5].

The natural history of gout includes four different phases: asymptomatic hyperuricemia, acute attacks, intercritical phase, and chronic tophaceous gout [6]. Initially, acute attacks (that typically resolve without therapy in 7 to 10 days) alternate with asymptomatic periods. Afterwards, if untreated, gout evolves in a chronic form with polyarticular attacks, symptoms present also between attacks and deposition of crystals (tophi) in soft tissues or joints, with the development of necrosis and fibrous proliferation and progressive joint destruction [1]. There is evidence that acute arthritis attacks are triggered by the deposition of MSU crystals in joints and soft tissues in which they act as "danger signals". This event leads to an inflammatory pathway with the activation of the inflammasome complex [nucleotide binding domain and leucin-rich repeat containing protein (NLRP)] with consequent release of interleukin (IL)-1β and other inflammatory mediators [1,7]. Synovial lining cells and phagocytes are responsible for further persistence of inflammation and tissue damage [1]. In a recent study, Pineda et al [8] reproduced the gout attack in 42 rabbits injecting crystals in their knee joints; then they compared clinical, histological, and ultrasonographic findings with the control group. The authors evaluated and described the early morphostructural changes observed by ultrasonography (US) during an acute gout attack.

Typical clinical and laboratory findings can induce the suspicion of gout, but the demonstration of MSU

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crystals in aspirated joint fluid or tophi is necessary for a definitive diagnosis [9]. However, this is not always possible or easy to perform.

Different studies have enhanced that gout management remains suboptimal and that there are few validated markers of disease activity [10-12]. This is an urgent problem to face. Indeed, chronic articular inflammation can lead to joint impairment and disability. Furthermore, uncontrolled hyperuricemia is associated with renal and cardiovascular disease [13-17] with overall increased morbidity and mortality [16,18].

Imaging modalities, such as conventional radiography (CR), musculoskeletal ultrasonography (US), computerized tomography (CT), and magnetic resonance (MRI) have several applications in the diagnosis, clinical monitoring and management of gout pathology, even if they are not included in the gout classification criteria [19]. Recently, the OMERACT Gout group reported the value of the different imaging modalities as measurement instruments for outcomes in studies of people with chronic gout, and evidenced which should be domains for imaging in gout and identified a research agenda about this issue [20].

Musculoskeletal US is an imaging tool characterized by a wide set of advantages. It is a not invasive, safe, easily accessible and a well-accepted imaging technique by the patient, relatively cheap and without any specific contra-indication [21]. Crystalline materials, present in joints or soft tissues, reflect ultrasound waves more strongly compared with surrounding tissues and are thus are easily distinguishable. Differently from the others imaging modalities, US can be useful for the diagnosis and management of gout from the initial manifestations of the disease.

Nowadays, the role of US in the detection of synovial and cortical bone lesions in rheumatoid arthritis (RA) is well established [22-25]. Different studies have demonstrated its capability to show both inflammatory and structural damage lesions in patients affected by osteoarthritis (OA) [26-29]. Moreover, its role is now more defined in the assessment of joint and soft tissue involvement in patients affected by connective tissue diseases (CTD) [30]. At the same extent, the usefulness of US in gout is progressively increasing. The aim of this review is to report the current available data present in the literature regarding the role of musculoskeletal US in the assessment of patients affected by gout.

US findings in gout

According to the literature, the US findings in gout can be differentiated in specific and non-specific signs of the disease [31,32]. Typical structures for MSU deposits are: hyaline cartilage, synovial fluid, bone, tendons, and soft tissues.

Non specific findings

Inflammatory abnormalities (joint effusion and synovial hypertrophy) and structural lesions (bone erosions) can be detected in gout patients; however, they are not specific for this condition [31,32]. *Joint effusion* is defined as an abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible but does not exhibit a Doppler signal; *synovial hypertrophy* appears as an abnormal hypoechoic intraarticular tissue that is not displaceable and is poorly compressible and may or not exhibit hypervascularisation with Doppler techniques [33]. Joint effusion is a frequent finding in gout and the presence of hyperechoic spots within effusion may be suggestive for the disease, being related to the presence of crystals aggregates. These aggregates have less than 1 mm and, during the examination, when pressing the probe on the surface of the examined structure, they float inside the joint realizing a characteristic "snowstorm appearance" [34,35]. Using US it is possible to identify joints with effusion and to perform US-guided aspiration with the aim of identifying crystals at synoval fluid analysis, which is considered the gold standard for the diagnosis [9]. Synovial hypertrophy and hypervascularisation can be also detected and, even though they are non specific findings, the possible presence of hyperechoic spots or cloudy areas in the synovium are strongly evocative for gout [34]. The presence of power Doppler signal indicates, as well as in the other forms of arthritis, active inflammation. It is sometimes possible to detect it even in clinically non inflamed joints, having the possibility to highlight a subclinical state of inflammation. Moreover, it has been demonstrated that the signal may disappear after treatment [32,36]. *Bone erosions* are defined as intra-articular discontinuity of the bone surface in two perpendicular planes [33]. They are present in the late stage of the disease and their presence correlates directly with the number of acute attacks, duration of disease, and presence of tophi. Characteristic sites for erosions are represented by the medial aspect of the first metatarsophalangeal joint, that is the most frequent, and the metacarpophalangeal joints [37,38]. Gout erosions cannot be differentiated from other erosive inflammatory arthropathies and no specific scoring systems, different from those used in RA, have been reported [32,39].

Specific signs of gout

The three different features that are considered as characteristic signs of gout are: ***double contour sign, aggregates*** and ***tophi.*** Recently, OMERACT definitions for gouty lesions have been published [40].

Double contour sign (DCS) is defined as an abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation, irregular or regular, continuous or intermittent, that can be distinguished from the cartilage interface sign [40]. This is due to the fact that MSU crystallize on the superficial margin of the cartilage so crystals deposits are mainly located on the superficial margin of the hyaline cartilage; contrarily, hyperechoic spots within the cartilage layer are suggestive for calcium pyrophosphate deposits [41]. DCS is considered one of the most specific features of this pathology; according to the evidence this finding has a sensitivity of 46.3 % and a specificity of 99% [42-45]. It is more frequently detected in symptomatic joints, particularly at the level of the metatarsophalangeal (especially the first) and metacarpophalangeal joints and at the hyaline cartilage of the knees. The visualization of DCS may be difficult in joints with limited width of the acoustic window for cartilage assessment as well as in osteoarthritic joint and in presence of effusion, which induces a posterior echo enhancement [31,35]. Interestingly, DCS has been found even in patients with asymptomatic hyperuricaemia [46,47] and it has been reported that it may disappear after therapy [48].

Aggregates, due to the deposition of MSU crystals in synovial fluids and other tissues, such as cartilage and soft tissues, are considered the landmark of gout. These aggregates reflect ultrasound beams more intensely than the surrounding tissues and their reflectivity is less influenced by the angle of insonation [31,32,35,49]. According to their different features (dimension, localization, and local reaction) and to the stage of the disease, three types of aggregates can be identified: hyperechoic spots, hyperechoic cloudy areas, and tophi [32,49]. *Hyperechoic spots* are bright dotted foci smaller than 1 mm, present within joint effusion (non specific), in hypertrophic synovium, or tophi (specific). *Hyperechoic cloudy areas* ("cottony images") [37] are aggregates smaller than 1 cm, usually homogeneous and without posterior acoustic shadow; they are considered as typical lesions of gout and are highly responsive to therapy [32,50]. *Tophi*, extracellular deposits of MSU surrounded by foreign body giant cells and mononuclear cells, forming a granuloma-like structure, can be found in any site and can be classified as soft, hard, and mixed [35,51,52]. Initially, tophi are soft on palpation, nodular, small, with homogeneous structure (soft tophi). After time, they become non-homogenous, bigger, and harder on palpation, frequently with calcifications inside and posterior acoustic shadow (hard and mixed tophi). The prevalence of tophi increases with the disease evolution [38].

Discussions

Different studies have recently addressed the role of US in gout. They evaluated not only the different lesions to be searched, but also the sites to be investigated [53,54] in order to improve the sensibility and specificity of the technique, the detailed changes that can be detected by US as well as the response to therapy. Naredo et al [53] demonstrated that the examination of 12 anatomical site searching for DC and aggregates had the best results in terms of sensitivity and specificity. Peiteado et al [54] recently underlined that knees and metatarsophalangeal joints are the most frequently involved sites and that the examination of those joints bilaterally can reveal the presence of DCS and aggregates in 97% of cases.

Recently, Ogdieet al [55] analyzed in a systematic literature review and meta analysis, the usefulness of different imaging modalities in gout in order to develop new classification criteria including imaging modalities. Eleven studies (7 on US) examining the sensitivity and specificity of imaging modalities in comparison to MSU crystals demonstration were included in this review. They concluded that imaging techniques, particularly US, could have a promising role in the diagnosis of gout and classification of patients with symptomatic disease. However, all the included studies were accomplished on a small number of patients with longstanding, established disease. Most of the studies were case-control reports. Finally, there was no homogeneity in the protocols and in the examined sites; further studies focusing on patients with early onset gout are necessary and standardization of the methodology for US is strongly needed.

Chowalloor et al [41] published the first systematic review focused on the validity, reliability, responsiveness, and feasibility of US-detected alterations not only in gout but also in asymptomatic hyperuricaemia. Eighteen studies were included: 14 regarding gout, 3 asymptomatic hyperuricemia, and one study with both conditions. The US findings studied in the review were tophi, articular cartilage abnormalities, soft tissue abnormalities, and bony lesions. US showed a good constructive validity in the detection of tophi when compared with MRI, as standard. It was also sensitive to change and demonstrated a satisfactory inter- and intra-observer reliability. In most cases, tophi were described as hyperechoic, with heterogeneous appearance with calcifications; sometimes they were grouped and had a poorly defined border and posterior acoustic shadowing. The heterogeneity of the description of the tophi in the different studies may underline the need for standardization of definitions to improve US validity and reliability. The presence of tophi was documented not only in symptomatic and not symptomatic gout, but also in

subjects with hyperuricaemia. Concerning cartilage, most studies referred to the DCS. DCS was found in gout as well as in subjects with hyperuricaemia. Inter-reader reliability offered excellent results in all the examined studies. The responsiveness was documented by the disappearance of the DCS after urate-lowering therapy. Regarding soft tissues abnormalities, such as joint effusion, synovial hypertrophy, intra-articular Doppler signal, intra-articular hyperechogenicity, tendon lesions, and soft tissue oedema, these were commonly found in the explored joints in gout as in all the other rheumatologic pathologies. In particular, US seemed to be useful in detecting active inflammation in gout by means of power-Doppler US in comparison with the clinical examination. Nonetheless, the presence of power-Doppler signal is sensitive rather than specific for the diagnosis of gout. The presence of findings indicating intra-articular MSU crystal deposition is widely addressed in the literature. This occurrence is highly suggestive of gout, however, without concordant results. US seems also capable of detecting erosions and demonstrated that it was a valid tool compared with MRI and CR. Indeed, it resulted in being even more sensitive, but less specific, than CR. Responsiveness of US to erosions was not reported when reliability was excellent.

Several aspects arise from the systematic review of Chowalloor et al [14] demonstrating that US is a promising tool in the diagnosis and management of gout. Nonetheless, a number of limitations are still present.

In terms of responsiveness, recently Ottavianiet al [56] developed a new study to determine the ability of US to show decrease or disappearance of urate deposits in gouty patients requiring urate-lowering therapy (ULT). They studied 16 male patients. Serum uric acid levels and US examination of knees and first metatarsophalangeal joints were registered at baseline and after six months of ULT. The four patients who had not achieved the target level of uric acid, showed a persistence of US features. Among the remaining 12 patients, US abnormalities (tophi or DCS) disappeared or decreased in all but one who had a stable DCS. The correlation between the whole US examination and uric acid level was excellent. This study confirmed that US correlates with efficacy of ULT, showing disappearance of specific signs of disease. Thus, it can be a useful tool not only in the diagnosis of gout but also in the follow up.

Peiteado et al [57] recently evaluated changes of Doppler signal during ULT in 24 patients. Knees and the first metatarsophalangeal joint were evaluated by US at baseline and at one and two years of follow up. Doppler US findings showed significant improvement after ULT in gout patients. Interestingly, Doppler signal persistence after two years of treatment was still evident, suggesting that current treatments are probably not effective.

Clinical diagnosis of gout is sometimes difficult and the role of US in the assessment of gouty patients is increasing. Taylor et al [58], in a recent study that included 938 patients with at least one tophus or one swollen joints, aimed to determine the most accurate clinical, laboratory, and imaging features, to differentiate patients with or without gout. They discriminated 10 key features; particularly, they showed that US findings added discriminating value and should be included in new and more accurate classification criteria.

US has another important role in the diagnosis of gout. As described, the direct visualization of crystals in synovial effusion, biopsies, or tophi is the gold standard diagnostic tool [9]. US can identify the site to perform the aspiration or the biopsy and can make the procedure easier and safer. Slot et al [59] recently reported the results from 9 consecutive patients newly suspected of having gout, with no effusion or tophi, who underwent dry needle synovial tissue aspiration in order to detect MSU crystals. Crystals were found in 8 of the 9 patients; no adverse effects were described. Usefulness of US is thus supported also in this field.

Moreover, intraarticular corticosteroid injection is considered an effective and safe therapeutic option in acute gouty arthritis, when nonsteroidal anti-inflammatory drugs and oral therapy are not tolerated, not effective, or contraindicated. US guidance enables a more accurate and safe procedure. Ho Kang et al [60] reported their experience in 21 patients with acute gout attack involving the first metatarsophalangeal joint, unilaterally. US was more sensitive than CR in detecting erosion and tophus-like lesion. US-guided intraarticular corticosteroid injection allowed a reduction of pain after 48 hours and there were no adverse events in none of the patients.

Finally, a few studies were focused on inter- and intra-observer reliability and feasibility was not addressed at all. This may lead to the perception of US as a highly user-dependent technique, possibly requiring a discrete amount of time especially in those cases with multiple joints and lesions.

The standardization and validation of US abnormalities is of fundamental importance in order to adopt US as a reference imaging method for gout diagnosis.

Conflict of interest: none

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