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EDITORIAL

From forgotten to frontline: the new era of crystal diseases?

Bürgisser N[1,2], Lauper K[1,3]

Crystal diseases, particularly gout and calcium pyrophosphate deposition disease (CPPD) are the most prevalent cause of inflammatory rheumatism in adults. Gout was first described in ancient Egypt, while CPPD was formally identified over 60 years ago. Gout remains a major public health concern, affecting 55.8 million people globally, with cases projected to reach 95.8 million by 2050[1]. CPPD is prevalent, especially in older adults, but its true incidence remains unclear as current estimates rely mostly on radiographic CPP deposition, which lacks sensitivity, specificity, and correlation with clinical disease[2]. Despite their long history and significant clinical burden, research and advances in this field has been relatively limited comparatively to other rheumatologic diseases until recently.

The growing availability of ultrasound and advanced imaging techniques has significantly improved the diagnosis of gout and CPPD. The new EULAR recommendations[3] on imaging in crystal diseases emphasize the role of ultrasound and dual-energy CT (DECT), making them sufficient for diagnosing gout in the absence of joint aspiration, when characteristic features (e.g. double contour sign, tophi) are present. Similarly, ultrasound of wrists, knees and affected joints is recommended for detecting CPPD crystals, further enhancing its role as a key diagnostic tool in clinical practice.

Traditionally, gout management emphasized dietary modification, particularly a low-purine diet. However, the influence of dietary factors on the long-term clinical course of gout remains uncertain. A recent study showed that dietary factors have only a modest effect on serum urate, contributing to just 0.3% of its variability[4]. Indeed, hyperuricemia is largely driven by genetic factors, with the strongest impact coming from those affecting urate transporters, and more recently discovered epigenomic changes[5], which increase the innate immune response to monosodium uric acid crystal. Given the strong association between gout and cardiometabolic comorbidities, dietary recommendations should thus be integrated into a broader health strategy rather than the primary focus. Urate-lowering therapy (ULT) should remain the cornerstone of treatment.

Despite effective and affordable drugs treatments, there remains an unmet need for new treatments to address the limitations of current therapies. Challenges include the lack of suitable options for patients with organ failure (e.g., severe chronic kidney disease), treatment-related risks (e.g., uricosuric-related lithiasis or flares triggered by ULT), dose titration of ULT challenges, or uricase-related autoantibodies development. Encouragingly, several novel therapies are currently under investigation in phase 1 to 3 clinical trials, targeting diverse mechanisms such as renal urate transporters URAT-1 or OAT4, intestinal excretion of urate, or innovative inflammasome targets[6]. Tiguloxistat, a novel xanthine oxidase inhibitor, demonstrated strong serum urate reduction even at low doses in a phase 2 trial, potentially minimizing the need for dose titration. To reduce antibody development in patients receiving uricase, co-administration of methotrexate improved the response rate to pegloticase and reduced infusion reactions, while a nanoparticle-based approach showed no added benefit and was associated with higher flare and infusion reaction rates[7].

Already available non-gout treatments, such as sodium-glucose co-transporter 2 inhibitors (SGLT-2-i), could also play a role in improving gout outcomes and managing comorbidities frequently associated with gout. Initially approved for diabetes, they are now recognized for treating heart failure and preventing the progression of chronic kidney disease. They reduce hyperuricemia and gout flares, likely through uricosuric and possibly anti-inflammatory effects[8]. Given the strong association of gout with diabetes, cardiac and renal comorbidities, SGLT-2-i may play a crucial role in addressing both gout and its related diseases[9].

Recent evidence has shown that gout patients face a higher risk of cardiovascular events, especially in the two years after flares, independently of their cardiovascular factors or urate levels[10]. At the same time, colchicine – long used in gout for flare treatment and prophylaxis - is increasingly recognised for cardiovascular benefits, particularly in patients with established

[1] Division of Rheumatology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland.
[2] Division of General Internal Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland.
[3] Geneva Center for Inflammation research, Department of Medicine, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Correspondence to: Nils Bürgisser
E-mail: nils.burgisser@hug.ch

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atherosclerotic cardiovascular disease, leading to its recent FDA approval for this indication[11]. Furthermore, an English observational study found that colchicine use alongside ULT initiation was associated with fewer cardiovascular events when used, further supporting its use in gout prophylaxis and reinforcing that flares are not benign[12].

While these developments offer hope for better treatments, gout is still often underdiagnosed and undertreated, and new therapies alone won't solve these gaps in care. Despite clear treatment recommendations for ULT, gout remains poorly managed, especially in racial and ethnic minorities, indigenous population and female[13]. Barriers include patient-related factors (stigma, low adherence) and physician-related gaps in diagnosis and management[14]. The COVID-19 pandemic further disrupted medical education and healthcare access, likely worsening underdiagnosis [15]. Improving patient outcomes will require not only the development of novel therapies but also better implementation of existing treatments.

For CPPD, research has lagged behind other forms of arthritis, largely due to the absence of validated classification criteria for symptomatic CPPD, which has hindered epidemiological studies and clinical trials. This long-standing gap was finally addressed with the development of the ACR/EULAR classification criteria for CPPD[16].

Analyses of the international rheumatology cohort used for the development of these classification criteria provided new insights into symptomatic CPPD phenotypes[17]. The study confirmed the significant heterogeneity of CPPD, with over half experiencing recurrent flares and a quarter developing persistent inflammatory arthritis. While there was significant phenotype overlap, distinct profiles emerged. Recurrent acute CPP crystal arthritis was linked to longer disease duration, suggesting progressive disease in some cases. Chronic CPPD with persistent inflammation correlated with specific osteoarthritis patterns, particularly in the wrists, metacarpophalangeal, and scapho-trapezo-trapezoid (STT) joints, but was less frequent in those with metabolic or familial risk factors. Crowned dens syndrome was more common in men and associated with STT joint osteoarthritis and widespread chondrocalcinosis.

EULAR developed guidelines on CPPD nomenclature in 2011, more than 14 years ago[18]. Nevertheless, confusion persists among clinicians and researchers over CPPD terminology, with "chondrocalcinosis" often misused for both flares and radiographic deposition[19]. To address this well-recognised issue, the Gout, Hyperuricaemia, and Crystal-Associated Disease Network is revising the nomenclature—but will it be widely adopted this time?

To date, no treatments have been shown to effectively dissolve CPP crystals, and management primarily focuses on symptom and inflammation control. A recent open-label RCT, COLCHICORT, found similar efficacy in term of pain relief at 24 hours between colchicine and prednisone, though more patients in the colchicine group experienced diarrhea (a quarter of patients), which may limit its use[20]. Other treatments, including methotrexate, IL-1, hydroxychloroquine, magnesium, have been studied, but significant methodological limitations—such as small sample sizes, lack of blinding, and reliance on retrospective data—make their effectiveness uncertain. While IL-1 inhibition targets the primary inflammatory pathway in CPPD via the NLRP3 inflammasome, emerging evidence suggests that IL-6 also plays a role. In a retrospective analysis of 55 patients with chronic CPPD or recurrent flares unresponsive to IL-1 inhibitors, IL-6 inhibition improved pain in nearly two-thirds, though 40% discontinued due to inefficacy or adverse effects[21].

CONCLUSION

Despite their long history, crystal diseases remain under-researched. Advances in imaging, genetics, and targeted therapies are reshaping gout and CPPD management, yet significant challenges persist. Despite effective therapies, gout continues to be inadequately treated, particularly in underserved populations, while CPPD research is finally progressing, with new classification criteria and emerging therapies. However, confusion in nomenclature and lack of crystal-dissolving treatments persist. Better implementation of existing treatments and sustained research efforts are essential to improve outcomes for these common yet often neglected diseases.

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