gout, urate, and crystal deposition disease

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Editorial

Gout, Urate, and Crystal Deposition Disease: Launch of the First Journal Dedicated to a Rapidly Growing Field

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1. Context

Gout and crystal deposition-associated disorders are among the leading causes of inflammation and arthritis throughout the world. Gout is the most common form of inflammatory arthritis, affecting over approximately 40 million people globally [1], including nearly 10 million in the US alone [2]. Historically referred to as "the disease of kings", the causes and mechanisms of gout, its comorbidities, and related crystal deposition diseases have been poorly understood over the centuries. However, over the last 20 years, research in this field has markedly expanded. The growth of this work has been in step with the increased prevalence and awareness of crystal-associated inflammatory diseases globally, as well as the recognition that hyperuricemia is directly linked with not only gouty arthritis, but also associated with diseases of major organ systems. Concurrently, the field has expanded to include more disciplines, including genomics, nephrology, cardiology, endocrinology, urology, and advanced imaging.

This journal is intended to publish a spectrum of research in the field, encompassing basic-translational research to epidemiology, clinical, and clinical-translational research. The publications will inform not only those primarily involved in research, but also clinicians who are actively managing patients. The journal will focus on the epidemiology, pathophysiology, imaging, diagnosis, treatment, and outcomes of gout, hyperuricemia, and degenerative and inflammatory calcium crystal arthropathies (including joint disease due to calcium pyrophosphate crystal (CPPD) and basic calcium phosphate crystal deposition). Related subject areas will include renal, vascular, and other extra-articular tissue sequalae of crystal deposition disorders. The foundation of the journal will be high-quality, peer-reviewed, basic, basic-translational, epidemiologic, and clinical-translational studies, including clinical trials. In addition, G-CAN (Gout, Hyperuricemia and Crystal-Associated Disease Network) annual research symposium abstracts, as well as a wide array of reviews and editorials, will be published in this journal. The range of investigative work presented in the journal will not only be international, but also both inter- and multidisciplinary.

Researchers from the fields of gout, crystal-associated arthritis, hyperuricemia, and urate biology are now well organized in international societies. The last decade has seen the emergence and rapid growth of G-CAN, the parent society of this journal. In addition, other networks in the field have grown in membership and recognition, including the European Crystal Network [3] and the Asia-Pacific Gout Consortium. In step with this global growth, outstanding publications in gout, hyperuricemia, urate biology, and crystal deposition disease are gaining increased attention and are attracting new researchers to the field. Furthermore, the quantity of related publications has increased approximately 100%

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in the previous decade. Publications linked to PubMed with key words such as gout, uric acid/urate, hyperuricemia, and allopurinol (a common treatment for gout) are shown in Figure 1. In comparison, publications on osteoarthritis (which can also be regarded as an underserved research area of rheumatic diseases) also increased by a similar proportion; however, publications on rheumatoid arthritis have increased by only approximately 50%.

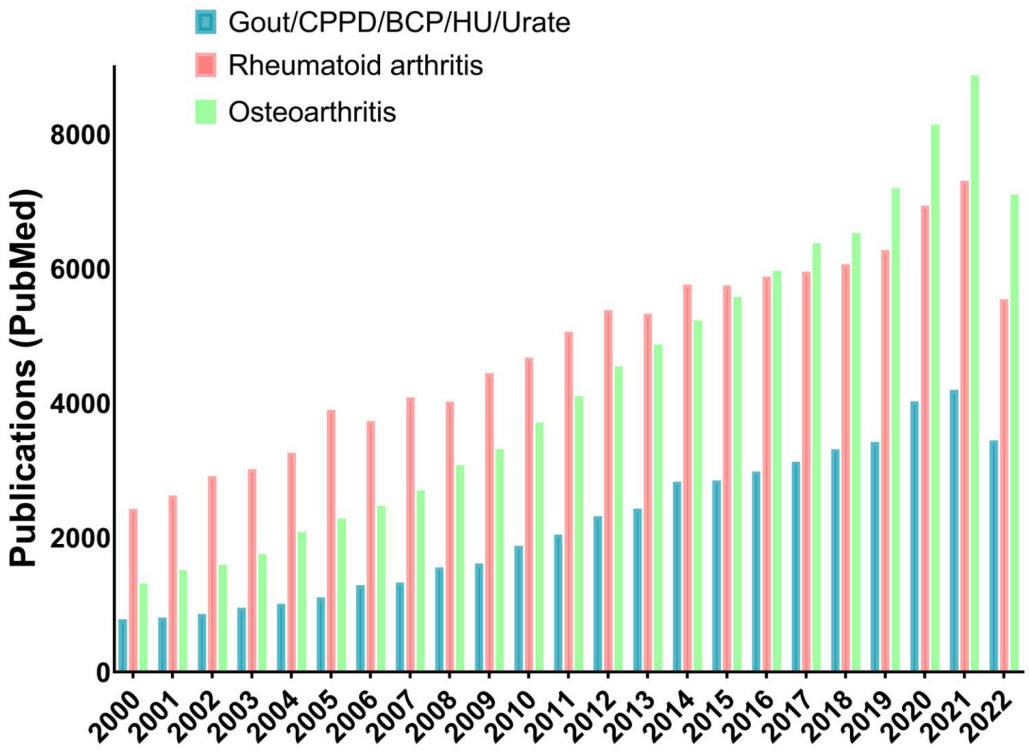

Figure 1. Number of publications referenced in PubMed since 2000 in the fields of crystal deposition diseases, rheumatoid arthritis and osteoarthritis.

International efforts are being made to standardize research and patient management in the field, many of them endorsed by G-CAN [4–7] and/or at the initiative of its members, including a consensus on the nomenclature of gout [8,9] and CPPD (ongoing), establishing the first classification criteria for CPPD [10,11], and identifying key outcome measures for CPPD through the OMERACT (Outcome Measures in Rheumatology) [12]. These collective endeavors will further raise the standards and, eventually, the volume and the quality merited by this field of research. The products of research in this field should ultimately meet the expectations of the numerous patients affected with crystal deposition diseases and their clinical care providers who will prescribe the advances in treatment. This new research needs a platform that is able to cover the full spectrum of the work performed in the field. The new *Gout, Urate and Crystal Deposition Disease* journal, a product of the G-CAN society, aims to disseminate this exciting research to the world.

2. Why Launch the First Journal in Gout, Hyperuricemia, Urate Biology, and Crystal-Associated Disease?

Research on diseases related to urate and crystal deposition diseases is largely relevant not only to general rheumatology journals, but also to other specialty journals. Many of these journals have a scope that includes coverage of this field of research, but they only sporadically publish papers on the topic. Additionally, today, it is unconscionable that gout management remains far from optimal globally, that we do not know how many patients are affected with calcium pyrophosphate deposition disease (CPPD), and that we have not established if asymptomatic hyperuricemia is pathological or not. These are only a few of

the questions surrounding urate biology and crystal deposition diseases that are far from adequately addressed.

The rise in numbers of publications on gout and closely related topics alone (Figure 1) is only the beginning of a wave of discovery and innovation. A 2021 bibliometric analysis of hyperuricemia global research trends [13] predicts that, based on current growth trends, the number of publications in this field will more than double, and hyperuricemia, gout, and their comorbidities will become the next "hot spot" for future research and publication. The analysis also predicts that, as more information about the mechanism of crystal deposition disorders is uncovered, the field will expand to include more disciplines, such as cardiology, endocrinology, and urology.

3. What Unmet Research Areas in Crystal Deposition Disease Do We Envisage? Some Crystal Ball Gazing

Table 1 lists various research areas that we consider unmet in gout, urate biology, and crystal deposition disease. Some areas expand on recent significant advances. For example, that a recent gout flare increases the risk of cardiovascular events and associated mortality [14] and the implication of the clonal hematopoiesis of indeterminate potential pathway in gout [15]. The role of the gut microbiome in systemic urate homeostasis and the regulation of gout-associated inflammation is gaining increased interest [16]. Broader areas of unmet needs include factors controlling crystal formation, the molecular pathogenesis of a gout flare, disentangling the causal relationship(s) between crystal disease and associated comorbidity, and identification and evaluation of new molecular targets in the prevention and management of flares. We welcome research papers addressing these unmet needs.

Table 1. Research in crystal arthropathy, now and in the future.

Recent Advances -> New Research Areas	Broad Areas of Unmet Needs
Recent gout flare increases risk of cardiovascular event [14]	Role of the articular environment and extracellular matrix in urate metabolism and monosodium urate crystal deposition
Poor urate control and lack of urate-lowering therapy worsen cardiovascular disease	The molecular pathogenesis of the gout flare and tophus deposition
Colchicine is effective in prophylaxis against major cardiovascular events [17]	Disentangling the causal relationship(s) between crystal disease and associated comorbidity
SGLT2 inhibitors are uricosuric, preventive for incident gout [18], have better outcomes for gout with diabetes, and have renal protective effects	Factors driving differences in pathogenesis of crystal disease between men and women
Allopurinol/febuxostat reach target in the majority of gout patients and improve outcomes with appropriate dosing [19,20]	Risk factors for crystal deposition disease in non-European populations
Febuxostat cardiovascular safety comparable to allopurinol [21]	The role of epigenomic reprogramming in immune response to crystals
HLA-B*5801 and ABCG2 pharmacogenomics	The pathogenesis and epidemiology of non-MSU crystal-mediated crystal deposition disease, including genetic and genomic studies
Gut microbiome manipulation robustly affects urate level [16]	Identification of biomarkers to identify patients at increased risk of flares
The clonal hematopoiesis of indeterminate potential pathway implicated in gout [15]	The pathogenic role of calcium pyrophosphate and/or basic calcium phosphate crystals in osteoarthritis onset and progression

Table 1. *Cont.*

Recent Advances -> New Research Areas	Broad Areas of Unmet Needs
Association of the blood metabolome with gout [22]	Should imaging outcomes guide gout treatment (ULT and prophylaxis)?
Association of the monosodium urate crystal burden assessed with advanced imaging techniques and gout flares, comorbidities, and mortality [23]	Treatments capable of achieving calcium pyrophosphate and basic calcium phosphate crystal dissolution and inhibiting crystal deposition
Dual-energy computed tomography and photon-counting computed tomography are able to discriminate intra-articular calcium crystal types [24]	Trials demonstrating the efficacy of any treatment to control the acute and/or chronic inflammation induced by calcium pyrophosphate crystals

We will publish papers on essential methodologies in this field, and align with workshops at our annual research symposium. This will help standardize approaches and to introduce those new to the field to the best approaches to investigate crystal arthropathy. Possible examples are animal models of hyperuricemia and crystal arthritis, imaging and tophus monitoring outcomes, flare reporting, design of outcomes studies, omic approaches, and epidemiology, including genetic epidemiology.

In view of the growing research and investigator community in this field, we are filling an unmet need for a central hub to publish quality, peer-reviewed articles on gout and crystal arthropathy. We aim to help broaden the interdisciplinary community that will contribute further advances in this area. Therefore, we are establishing this G-CAN open access journal for original research, review, and editorial publications in this field, dedicated exclusively to gout, urate biology, and crystal arthropathy. Our journal, *Gout, Urate Biology, and Crystal Arthropathy*, launching in 2023, is the official journal of G-CAN (Gout, Hyperuricemia and Crystal-Associated Disease Network).

4. About G-CAN

G-CAN is an international volunteer organization dedicated to creating research and education initiatives to fill the gout, urate biology, and crystal-associated diseases knowledge gap. It is incorporated as a USA charitable foundation 501c3. With more than 200 members worldwide from a variety of disciplines, we are one of the largest organizations furthering research in the field of gout and crystal-associated diseases. Founded in 2015 by Drs. Robert Terkeltaub and Hyon Choi, G-CAN is a unique and rapidly growing global research network. The G-CAN platform includes an annual international research symposium with more than 200 attendees, 20–30 annual abstract submissions by early career investigators, an annual group of "Year in Review" sessions that summarize and discuss major developments in the field, and a total of ~40 presenters annually. G-CAN has an internet presence with a website and an active and engaged social media following.

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