First clinical practice guideline for renal hypouricaemia: a rare disorder that aided the development of urate-lowering drugs for gout

It is of interest that research on patients with renal hypouricaemia (RHUC) has provided new insights into urate handling and has resulted in the identification of therapeutic molecular targets for gout and hyperuricaemia. We hereby summarize the first clinical practice guideline (CPG) for RHUC [1] and describe three essential points as to why improved understanding of RHUC will also identify novel molecular targets for urate-lowering drugs, clarify the physiological role of urate and provide clues to clinical questions on gout.

Gout is a common disease characterized by intermittent flares and/or subcutaneous tophi that are sequelae of sustained hyperuricaemia. Three representative urate transporters, URAT1/SLC22A12 [2, 3], GLUT9/SLC2A9 [4, 5] and ABCG2 [6] play important roles in urate handling. The former two renal urate reabsorption transporters are target molecules of uricosuric drugs such as benz bromarone [2]. These were identified from genetic analyses of RHUC patients [2, 4]; dysfunctional variants of their genes eliminate renal urate reabsorption, resulting in RHUC. RHUC patients therefore typically show low serum uric acid (SUA) levels and high renal urate clearance. Depending upon the causative genes, i.e. URAT1/SLC22A12 or GLUT9/SLC2A9, RHUC is now divided into two types called RHUC types 1 (RHUC1: MIM 220150) and 2 (RHUC2: MIM 612076), respectively [7]. Selective urate reabsorption inhibitors (SURIs), including lesinurad and dotinurad, which target URAT1, have been developed based on these findings. Importantly, some patients cannot be classified despite genetic analyses, suggesting novel RHUC mechanisms and therefore novel target molecules for gout treatment. Consequently it is vital to promote research on RHUC, as this will lead not only to elucidation of its pathophysiology, but to the development of new treatments for gout and hyperuricaemia.

Although RHUC is a relatively rare hereditary disorder globally, it is frequently found in Japanese [4], Jewish [5] and European Roma [8, 9] populations. Up to ~0.3% of the Japanese population is estimated to have RHUC, a number similar to that of haemodialysis patients in Japan. RHUC is, however, little known, even to healthcare professionals: it is generally believed that “the lower your SUA, the better”. This may be partly because RHUC itself is asymptomatic and there have hitherto been no established guidelines on how to arrive at a definitive diagnosis. RHUC can present with exercise-induced acute kidney injury (EIAKI, also known as acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE)) and urolithiasis [1].

Our world-first CPG was developed to facilitate standardized diagnosis and treatment of RHUC patients, to support awareness-raising and education for healthcare professionals and to provide a solid foundation for further research. It complies with the Medical Information Network Distribution Service (MINDS) guideline development methodology [10], which emphasizes evidence-based medicine (EBM) and is designed to help patients and healthcare professionals make optimal clinical decisions. This CPG contains comprehensive information about RHUC, including its epidemiology, pathophysiology, clinical examination/diagnosis and complications, in addition to clinical questions and evidence-based recommendations. The CPG algorithm (Fig. 1) articulates clinical diagnostic procedures for RHUC, enabling physicians to make definitive diagnoses via simple blood and urine examinations. Statements with low evidence levels are complemented where appropriate by ‘consensus levels’ as expert opinions to assist healthcare professionals’ understanding. In the patient message section, a female mixed martial arts fighter who has long suffered from EIAKI explains how this open-access CPG will also help patients learn about and combat RHUC.

The clinical key to RHUC is its complications. EIAKI presents in young adults as severe loin pain, nausea and AKI after intense anaerobic exercise such as short-distance sprinting. Patients may show slightly elevated or normal creatinine kinase (CK) and do not have myoglobinuria; mildly elevated CK may result in a rheumatology referral. Recurrent hospital admissions from childhood are also seen. There is a study reporting 6.5% of RHUC patients as having EIAKI [3], while no studies report a move to long-term dialysis due to exacerbation to CKD. EIAKI appears to be caused by a lowered radical scavenger effect of urate in lowered SUA in RHUC patients, which aggravates the ischaemic effect activated by renal vasopressor factors due to oxygen radicals; however, its exact mechanism remains unclear. A few case reports have shown the effects of EIAKI prevention by a xanthine oxidoreductase (XOR) inhibitor, allopurinol [1], which inhibits oxygen radicals and urate synthesis. XOR inhibitors might therefore mitigate the onset of EIAKI due to decreased renal load by uric acid, although further studies are necessary. The CPG therefore states...
that we cannot definitively claim that XOR inhibitors should be administered to prevent EIAKI in RHUC patients and recommends their administration after considering their potential benefits and harms, especially in athletes and high-risk patients with a past history of EIAKI [1]. Urolithiasis appears common in this population, although its
prevalence is not precisely known; both urate and calcium oxalate stones have been reported.

However, most patients with RHUC are asymptomatic. To prevent patients from developing complications, physicians' advice such as to drink water before exercise and/or limit exercise has great clinical relevance for correct disease control.

The overall picture of RHUC remains unclear. For example, uric acid has an antioxidative effect, but no studies have been conducted on whether RHUC is associated with findings other than EIAKI or urolithiasis, such as carcinogenesis, neurodegenerative diseases or longevity.

It is still not fully known to what extent physicians can lower gout patients' SUA based on the principle of 'the lower, the better'. Progress toward answering this clinical question is likely to be based on clinical investigations with RHUC patients, since their SUA levels are typically <2 mg/dl (120 μmol/l).

Some RHUC patients are diagnosed by chance during health examinations and others are found after a diagnosis of EIAKI or urolithiasis. This CPG should help physicians to single out RHUC patients from among individuals with low SUA, which should assist with timely prevention and treatment. With the CPG as a starting point, the promotion of RHUC research should accelerate the discovery of novel treatments in related fields such as gout and hyperuricaemia.

**Collaborators**

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**Data availability statement**

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