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COMMENTARY

A proposal for identifying the low renal uric acid clearance phenotype

Praveen L Indraratna[1,2], Sophie L Stocker[3,4], Kenneth M Williams[1,2], Garry G Graham[1,2], Graham Jones[5] and Richard O Day*[1,2]

Abstract

Investigation of the genetic basis of hyperuricaemia is a subject of intense interest. However, clinical studies commonly include hyperuricaemic patients without distinguishing between 'over-producers' or 'under-excretors' of urate. The statistical power of studies of genetic polymorphisms of genes encoding renal urate transporters is diluted if 'over-producers' of uric acid are included. We propose that lower than normal fractional renal clearance of urate is a better inclusion criterion for these studies. We also propose that a single daytime spot urine sample for calculation of fractional renal clearance of urate should be preferred to calculation from 24-hour urine collections.

Introduction

Hyperuricaemia, defined as a plasma concentration of urate (used interchangeably with uric acid) greater than 0.42 mmol/L (7.0 mg/dL) [1], is the major risk factor for gout. Impaired renal clearance of urate, or 'under-excretion', accounts for up to 90% of hyperuricaemia cases. In the remainder, the mechanism is excessive production of urate due to purine synthetic enzymatic abnormalities, haematological malignancies [2] or dietary excess. Under-excretion and over-production of urate can co-exist [3].

Investigation of the molecular basis of low renal urate clearance ought to be conducted in individuals where low clearance has been proven but most studies have used hyperuricaemia alone as the inclusion criterion, thereby reducing the power of the study [4-7].

Simkin and colleagues proposed a spot morning urine test of urate excretion normalised to glomerular filtration rate (GFR) to identify 'over-producers' of urate [8]. We propose an amendment to the Simkin Index in order to focus upon abnormalities in renal tubular urate transport causal for 'under-excretion' of urate. We suggest that renal uric acid clearance be normalised to the individual's GFR, as estimated by the creatinine clearance, to give the fractional clearance of urate (FCU). FCU has been used in physiological studies but usually employing 24-hour collections of urine [3,6]. We propose that FCU calculated from spot urine samples be used as the inclusion criterion in studies examining the genetic basis for relatively low renal clearance of urate. A renal lesion(s) that reduces the ability of the kidney to clear uric acid, but not creatinine, will manifest as a low FCU relative to normal.

FCU is calculated using the formula:

$$FCU = \frac{U_{UA} \bullet P_{creat}}{P_{UA} \bullet U_{creat}}$$

By contrast, the Simkin Index does not include plasma urate concentrations:

$$Simkin\ Index = U_{UA} \bullet \frac{P_{creat}}{U_{creat}}$$

The concentrations of plasma and urinary creatinine (P_{creat}; U_{creat}) and urate (P_{UA}; U_{UA}) are readily obtained. Measurement of the volume of urine is not required, which is a significant practical advantage [8]. When calculated from a morning spot collection (9 to 11 a.m.), the Simkin Index was found to be reproducible, the coefficient of variation being ±20% in 19 normal males and closely correlated with their 24-hour urinary uric acid outputs [8]. We have found a coefficient of variation of FCU of ±7% from daytime spot urine collections in 12 healthy volunteers [9].

Under-excretion or low renal clearance of uric acid

Optimally, when searching for the molecular basis of the renal tubular lesion(s) responsible for reduced renal

*Correspondence: r.day@unsw.edu.au
[2]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, 2010, Australia
Full list of author information is available at the end of the article

clearance of uric acid, hyperuricaemic individuals with otherwise normal renal function or GFR should be studied. Renal impairment alone reduces the renal clearance of uric acid. FCU can determine the contribution of renal impairment to the reduced renal clearance of uric acid by adjusting for the individual's GFR. Also, FCU is superior to the measurement of the renal uric acid clearance alone because it is not affected by incomplete urine collections. A caveat is that as renal function declines the FCU tends to increase somewhat because the renal clearance of urate does not decline as rapidly as the creatinine clearance and GFR. In those with a GFR between 20 and 30 mL/minute, the mean FCU was 0.188 (n = 10) compared to 0.099 in those with normal renal function (n = 20) [7]. This effect of poor renal function should not be a drawback to using the FCU, as mechanistic studies would be better undertaken in those with normal GFR.

The genetic 'lesion'

Renal function (measured by GFR) of many hyperuricaemic individuals, especially in the early stages of their hyperuricaemia or in the absence of co-morbidities such as diabetes, is normal, indicating their FCU will be low compared to urate over-producers and most normouricaemic individuals. Hyperuricaemia is common, so there is a relatively common renal tubular lesion(s) manifest by an impaired ability of the kidneys to clear uric acid. This lesion likely has a genetic basis given that the heritability of relatively low FCU has been estimated to be 87% [10]. Increasingly, polymorphisms of genes encoding transporters relevant for uric acid tubular transport, such as *SLC2A9* and/or *ABCG2*, have been identified and are suspected of leading to low FCU [4-7,11]. Despite this, FCU has only rarely been used as the phenotypic expression of the activity of uric acid transporters in clinical studies exploring the genetic basis of hyperuricaemia. Vitart and colleagues [6] did not find a correlation between FCU and polymorphisms of *SLC2A9*; however, using FCU enhanced the power of the study to potentially discover relevant genetic polymorphisms. These subjects with normal GFR but low FCU provide the optimal cohort for studies elucidating the molecular and genetic mechanisms for hyperuricaemia due to abnormal renal tubular transport of urate.

Advantages of using FCU

In an individual who is hyperuricaemic and with renal impairment or who over-produces urate, FCU may be normal or increased [12]; that is, the mechanism for the hyperuricaemia does not include a genetically based, renal tubular transport defect. Employing the FCU will eliminate patients with these other causes of hyperuricaemia.

FCU is easily obtained in the clinical setting because a simple, random spot urine sample is sufficient for its calculation [8]. Collection of the spot sample in the morning is recommended [8] to account for any diurnal variation in renal function. In fact, FCU decreases during sleep when there is a state of relative dehydration associated with activation of the renin-angiotensin system. FCU is also reduced in some individuals with the metabolic syndrome, again possibly due to activation of the renin-angiotensin system, and is affected by gross changes in hydration status, increasing with significant water loading [13,14].

Graessler and colleagues [15] used 0.06 as the lower limit of normal FCU but it is unclear how this level was established and population studies, including individuals with renal impairment, are required to better establish normal ranges for FCU.

Conclusion

It is proposed that FCU represents a good phenotypic measure of the ability of the kidney to clear uric acid. A mid-morning spot urine sample in a normally hydrated individual replaces the inconvenient and often inaccurate 24-hour urinary uric acid excretion test. Population studies of FCU values with attention to demographics, co-morbidities, GFR and concomitant medications are needed. Use of FCU in genetic studies exploring risk factors for hyperuricaemia of renal tubular origin will provide more power to identify relevant associations, potential mechanisms and, ultimately, new therapeutic options.

Abbreviations

FCU, fractional clearance of urate; GFR, glomerular filtration rate.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Faculty of Medicine, University of New South Wales, NSW, 2052, Australia. [2]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, 2010, Australia. [3]Faculty of Pharmacy, University of Sydney, NSW, 2006, Australia. [4]Institute of Health Innovation, Faculty of Medicine, University of New South Wales, NSW, 2052, Australia. [5]Department of Chemical Pathology, Sydpath, St Vincent's Hospital, Sydney, NSW, 2010, Australia.

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