





Original Article

Utility of blood tests in screening for metabolic disorders in kidney stone disease

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Objectives

To determine the clinical utility of blood tests as a screening tool for metabolic abnormalities in patients with kidney stone disease.

Subjects and Methods

Clinical and biochemical data from 709 patients attending the Oxford University Hospitals NHS Foundation Trust for assessment and treatment of kidney stones were prospectively collected between April 2011 and February 2017. Data were analysed to determine the utility of serum calcium, parathyroid hormone (PTH), urate, chloride, bicarbonate, potassium and phosphate assays in screening for primary hyperparathyroidism, normocalcaemic hyperparathyroidism, hyperuricosuria, distal renal tubular acidosis (dRTA) and hypercalciuria.

Results

An elevated serum calcium level was detected in 2.3% of patients. Further investigations prompted by this finding resulted in a diagnosis of primary hyperparathyroidism in 0.2% of men and 4.6% of women for whom serum calcium was recorded. An elevated serum PTH level in the absence of hypercalcaemia was detected in 15.1% of patients. Of these patients, 74.6% were vitamin D-insufficient; no patients were diagnosed with normocalcaemic hyperparathyroidism. Hyperuricosuria was present in 21.6% of patients and hypercalciuria in 47.1%. Hyperuricaemia was not associated with hyperuricosuria, nor was hypophosphataemia associated with hypercalciuria. No patient was highlighted as being at risk of dRTA using serum chloride and bicarbonate as screening tests.

Conclusion

This study indicates that individuals presenting with renal calculi should undergo metabolic screening with a serum calcium measurement alone. Use of additional blood tests to screen for metabolic disorders is not cost-effective and may provide false reassurance that metabolic abnormalities are not present. A full metabolic assessment with 24-h urine collection should be undertaken in recurrent stone formers and in those at high risk of future stone disease to identify potentially treatable metabolic abnormalities.

Keywords

nephrolithiasis, metabolic assessment, blood tests, kidney stones, metabolic screening, #KidneyStones, #UroStone

Introduction

Kidney stone disease is a common condition that affects up to ~20% of men and ~10% of women in their lifetime, accounts for over 85 000 hospital episodes each year in the UK, and was estimated to cost the US \$3.79 bn in 2014 [1–3]. The aetiology of stone formation in the majority of cases is multifactorial and the result of a combination of poorly understood environmental and genetic influences [4].

However, in a minority of cases, a well-defined metabolic abnormality, such as primary hyperparathyroidism or distal renal tubular acidosis (dRTA), will be the underlying causative pathology [5]. National and international guidelines recommend that patients presenting with kidney stones undergo metabolic screening with blood tests, with the aim of identifying cases that require further investigation to make a diagnosis such as this [5–7]. However, currently there is no consensus as to which blood tests should be undertaken and

evidence to support these guidelines is limited [6]; consequently, there is wide variation in clinical practice.

In the UK, the National Institute of Health and Care Excellence (NICE) recommends that adults presenting with ureteric or renal stones undergo metabolic screening with a serum calcium blood test alone [6]; an elevated serum calcium level may indicate previously unrecognized hyperparathyroidism, granulomatous disease or malignancy [5]. The NICE committee was unable to identify any evidence to inform recommendations for metabolic blood tests in patients with kidney stones, but made note of the high prevalence of primary hyperparathyroidism in these individuals and the low cost of serum calcium testing [6,8–10]. In addition to serum calcium, the European Association of Urology (EAU) recommends that serum urate is checked routinely in emergency urolithiasis patients [5]. However, whilst evidence exists for the use of allopurinol in patients with hyperuricosuria and normocalciuria to reduce kidney stone events [11–14], data demonstrating an association of hyperuricaemia alone with kidney stone formation is limited and thus the EAU guidelines only advocate the use of xanthine oxidase inhibitors where hyperuricosuria exists [5,15,16]. The AUA suggests that, as well as serum calcium and urate blood tests, serum chloride, bicarbonate and potassium are routinely measured as part of an assessment for dRTA [7]. Patients with dRTA experience a hyperchloraemic hypokalaemic metabolic acidosis, which may be reflected by reduced serum bicarbonate and potassium levels in combination with an elevated serum chloride level [17]. The AUA also recommends that, where there is suspicion of primary hyperparathyroidism due to a 'high normal' serum calcium, serum parathyroid hormone (PTH) measurement should be undertaken to exclude normocalcaemic hyperparathyroidism [7]. Furthermore, alterations in phosphate homeostasis may be linked to kidney stone formation and, consequently, a subset of clinicians will routinely assess serum phosphate levels in nephrolithiasis patients with the aim of identifying those with hypophosphataemia who may be at risk of hypercalciuria due to reduced phosphate levels stimulating $1,25(\text{OH})_2$ vitamin D synthesis and enhancing intestinal calcium uptake [18,19].

In this study, we examined a large database of serum and urine biochemistries from individuals with kidney stone disease to ascertain the clinical utility of blood tests in screening for metabolic disorders in patients with nephrolithiasis.

Subjects and Methods

Study Population

Between April 2011 and February 2017, 709 patients attending the Oxford University Hospitals NHS Foundation

Trust for assessment and treatment of kidney stones were enrolled into the Oxford University Hospitals NHS Foundation Trust Biobank of Kidney Stone Formers. Patients were approached for recruitment into the Biobank regardless of the number of previous stone episodes or risk of future stone formation. All patients entering the Biobank were requested to provide serum and 24-h urine samples for analysis: 311 patients provided 24-h urine samples. Clinical data, including urological history and medical history, were recorded, along with details of serum and 24-h urinary biochemistry. Collection of clinical data was approved by the University of Oxford under the Oxford Radcliffe Biobank research tissue bank ethics (09/H0606/5+5). All patients provided written informed consent.

Reference Ranges

Reference ranges were defined as follows: serum calcium = adjusted serum calcium 2.2–2.6 mmol/L (local laboratory reference range) [20]; serum phosphate = 0.8–1.29 mmol/L [5]; serum urate = 119–380 $\mu\text{mol/L}$ [5]; serum potassium = 3.5–5.0 mmol/L (local laboratory reference range); serum chloride = 98–112 mmol/L [5]; serum bicarbonate = 20–30 mmol/L [21]; serum PTH = 1.3–7.6 pmol/L (local laboratory reference range); vitamin D insufficiency = serum 25-hydroxyvitamin D (25(OH)D) <50 nmol/L [22]; serum creatinine = 49–90 $\mu\text{mol/L}$ in women and 64–104 $\mu\text{mol/L}$ in men (local laboratory reference ranges); hypercalciuria = 24-h urinary excretion of calcium >5 mmol/day [5]; hyperuricosuria = 24-h urinary excretion of uric acid >4 mmol/day in women and >5 mmol/day in men [5].

Statistical Analysis

Individuals were excluded from analysis if previously diagnosed with hyperparathyroidism, granulomatous disease or dRTA, and where data were incomplete or if data appeared to have been entered into the database incorrectly. Fisher's exact tests were used to assess statistically significant differences between groups of categorical data. Linear regression analysis was undertaken to assess associations between groups of continuous data. All statistical analyses were undertaken using GraphPad PRISM software.

Results

In total, 497 men and 185 women were enrolled into the Oxford University Hospitals NHS Foundation Trust Biobank of Kidney Stone Formers. For 27 individuals, sex was not recorded. Details regarding patient demographics, stone history and biochemical data are shown in Table 1. Twenty-four-hour urine collection was undertaken in 265 patients. Twenty-four-hour urinary calcium excretion data were available for 256 patients, of whom 121 were found to be hypercalciuric (47.1%). Twenty-four-hour urinary uric acid

Table 1 Demographics, stone history and biochemical make-up of the Oxford University Hospitals NHS Foundation Trust Biobank of Kidney Stone Formers.

	Reference range	Number of patients with data available	Median	Interquartile range	Range
Age	—	565	56	45–68	22–92
Sex, <i>n</i>					
Men	—	499			
Women		182			
Number patient-reported previous stone episodes	—	468	2	1–3	0–30
Adjusted serum calcium, mmol/L	2.2–2.6	529	2.33	2.28–2.40	2.11–3.34
Serum phosphate, mmol/L	0.8–1.29	542	0.99	0.88–1.13	0.21–7.40
Serum urate, μ mol/L	119–380	544	339	282–403	25–664
Serum creatinine, μ mol/L	49–90 (women) 64–104 (men)	606	78	67–95	31–761
Serum bicarbonate, mmol/L	20–30	488	27	26–30	13–40
Serum chloride, mmol/L	98–112	462	104	102–106	2.31–112
Serum potassium, mmol/L	3.5–5.0	612	4.0	3.8–4.3	2.9–5.5
Serum PTH, pmol/L	1.3–7.6	496	4.7	3.2–6.6	0.8–20.5
Serum 25-hydroxyvitamin D, nmol/L	>50	413	50	33.7–69.0	<12.5–250.0
24-h urinary calcium excretion, mmol	<5	256	4.87	2.92–7.19	0.18–27.42
24-h urinary uric acid excretion, mmol	<4 (women) <5 (men)	208	3.1	2.29–4.26	0.56–28.86
24-h urine volume, mL	—	296	1830	1320–2395	200–6290

PTH, parathyroid hormone.

excretion data were available for 208 patients, of whom 45 were found to be hyperuricosuric (21.6%).

Utility of Serum Calcium Concentration to Identify Hyperparathyroidism, Granulomatous Disease or Malignancy

Serum calcium concentration was recorded in 529 patients: 373 men and 146 women. Sex was not recorded for 10 individuals. Three men (0.8%) and nine women (6.2%) were found to be hypercalcaemic (range 2.63–3.34 mmol/L, median 2.72 mmol/L). Nine of these patients had a PTH check at entry into the biobank (range 2.9–20.5 pmol/L, median 9.2 pmol/L) and serum PTH was raised in six cases. In total, nine patients (one man, eight women) were referred to endocrinology for further assessment, two were lost to follow-up and seven (1.3%) went on to be diagnosed with and treated surgically for primary hyperparathyroidism. Parathyroid adenomas were identified on histological analysis of all surgical specimens. Of the seven patients diagnosed with primary hyperparathyroidism, six were women; thus, 4.6% of the women and 0.2% of the men with kidney stones were diagnosed with primary hyperparathyroidism. Considering the three patients with hypercalcaemia who were not referred to endocrinology, one patient's serum calcium normalized when rechecked and no further data were available for two patients.

Utility of Serum PTH to Identify Normocalcaemic Hyperparathyroidism

Parathyroid hormone measurement was undertaken in 496 patients, of whom serum calcium level was evaluated in 494.

PTH level was raised (range 7.7–20.5 pmol/L, median 9.3 pmol/L) in 81 patients (16.3%) and, of these, 75 (15.1%) were not hypercalcaemic (range 2.11–2.58 mmol/L, median 2.32 mmol/L). Of these 75 patients without hypercalcaemia but raised PTH levels, 56 were vitamin D-insufficient (74.6%) and 15 were vitamin D-replete (20.0%); vitamin D status was unknown for four individuals. In the 15 vitamin D-replete patients, PTH normalized on repeat measurement in eight patients. Two patients were referred for endocrinological assessment, one was subsequently diagnosed with uric acid stones and the other with impaired calcium absorption secondary to chronic diarrhoea. Two patients continued urology follow-up with no further stone episodes reported at a minimum of 1 year; data were unavailable for three patients.

Utility of Serum Urate to Predict Hyperuricosuria

Serum urate was measured in 544 patients and 24-h urinary uric acid excretion data were available for 181 of these. Hyperuricaemia was detected in 185 patients (34.0%). Hyperuricosuria was not associated with hyperuricaemia

Table 2 Distribution of normouricaemia, hyperuricaemia, normouricosuria and hyperuricosuria in patients enrolled in the Oxford University Hospitals NHS Foundation Trust Biobank of Kidney Stone Formers.

	Normouricosuria	Hyperuricosuria
Normouricaemia	96 (53.9)	28 (15.7)
Hyperuricaemia	43 (24.2)	11 (6.0)

Percentage of individuals with phenotype with respect to all patients with normouricaemia or hyperuricaemia and urinary uric acid excretion data is shown in parentheses.

Table 3 Distribution of normophosphataemia, hypophosphataemia, normocalciuria and hypercalciuria in patients enrolled in the Oxford University Hospitals NHS Foundation Trust Biobank of Kidney Stone Formers.

	Normocalciuria	Hypercalciuria
Normophosphataemia	98 (44.3)	94 (42.5)
Hypophosphataemia	13 (5.8)	16 (7.2)

Percentage of individuals with phenotype with respect to all patients with normophosphataemia or hypophosphataemia and urinary calcium excretion data is shown in parentheses.

(Table 2; Fisher's exact test $P = 0.84$); hyperuricosuria was present in 30.9% of patients with normouricaemia and 28.2% of those with hyperuricaemia. Hyperuricaemia was not predictive of hyperuricosuria (positive predictive value 0.20), nor was normouricaemia an accurate indicator of normouricosuria (positive predictive value 0.77). Furthermore, on linear regression analysis, there was no correlation of serum urate concentration with 24-h urinary uric acid excretion ($r^2 = 0.006$).

Utility of Chloride, Bicarbonate and Potassium to Identify Distal Renal Tubular Acidosis

Serum chloride, bicarbonate and potassium data were available for a total of 427 patients, and urinary pH was available for only six of these. Reduced bicarbonate levels were detected in seven patients, none of whom had an elevated serum chloride or a reduced serum potassium level. No patients were found to be hyperchloraemic.

Utility of Serum Phosphate to Predict Hypercalciuria

Serum phosphate data were available for 542 patients. Twenty-four-hour urinary calcium excretion data were available for 231 of these patients, of whom 112 were hypercalciuric. Hypercalciuria was not associated with hypophosphataemia (Table 3; Fisher's exact test $P = 0.56$); hypercalciuria was present in 49.0% of patients with normophosphataemia and in 55.2% of those with hypophosphataemia. Hypophosphataemia was not predictive of hypercalciuria (positive predictive value 0.55). Furthermore, on linear regression analysis, there was no correlation of serum phosphate concentrations and 24-h urinary calcium excretion ($r^2 = 0.01$).

Discussion

This study assessed the clinical value of undertaking blood tests to screen for metabolic disorders in patients presenting with kidney stones. Primary hyperparathyroidism has been reported in 0.5–5% of the stone-forming population [8–10]. We observed that primary hyperparathyroidism was detected in approximately 1% of all stone-formers when an elevated serum calcium level was used to prompt further

investigations. However, this diagnosis was made in <0.5% of men but >4% of women presenting with kidney stone disease. In the population studied, serum PTH measurement in 467 patients did not result in any diagnoses of normocalcaemic hyperparathyroidism. Our findings suggest that clinically significant normocalcaemic hyperparathyroidism will be missed in a very small number of patients with kidney stones when screening for hyperparathyroidism is undertaken with serum calcium alone. However, vitamin D insufficiency, which was common in those with elevated PTH in this study, can mask primary hyperparathyroidism. Further studies investigating alterations in PTH following vitamin D supplementation in vitamin D-deficient stone-forming populations would be beneficial [23]. Normocalcaemic hyperparathyroidism may be linked to renal stone disease and therefore, in individuals with recurrent nephrolithiasis or at high risk of future stone disease, serum PTH measurement may be a useful component of a full metabolic assessment [24].

In keeping with previously published results, we found that hyperuricosuria was present in approximately 20% of patients with kidney stones [25,26]. We demonstrated that serum urate should not be used as a screening test to identify individuals at risk of hyperuricosuria and that in this heterogeneous population there is no association of hyperuricaemia with hyperuricosuria. Hyperuricaemia was not predictive of hyperuricosuria, and normouricaemia was not a reliable indicator of normouricosuria.

Hyperuricosuria is a risk factor for the formation of both calcium oxalate and uric acid stones [27,28]; however, urinary pH is more important in the formation of uric acid stones than urinary uric acid concentration [27]. In the case of calcium oxalate stones, dissolved uric acid salts are reported to reduce the solubility of calcium oxalate, thus increasing the chance of stone formation [28]. Allopurinol has been shown to be effective in reducing urinary uric acid excretion and number of stone events in individuals who form calcium oxalate stones with normocalciuria and hyperuricosuria [12]. However, no reduction in stone risk has been identified in studies that did not limit enrolment to individuals with normocalciuria and hyperuricosuria [12,14]. Our findings suggest that the opportunity to treat a considerable number of hyperuricosuric patients will be missed if a normal serum urate level is used to infer normal urinary uric acid excretion. Clinicians should be mindful that measurement of serum urate may be useful where there is a history of symptomatic arthropathy to facilitate the diagnosis and management of gout, which has been linked to the formation of uric acid stones [7,29,30].

dRTA may be acquired or inherited and is reported to be present in up to 8% of kidney stone patients [31]. In our dataset of 427 patients, none was identified to be at risk of

dRTA on the basis of measurement of serum chloride, bicarbonate and potassium concentrations, suggesting that these investigations are ineffective tools in screening for this disorder. dRTA is caused by defective hydrogen ion secretion by α -intercalated cells in the distal renal tubule, resulting in an increase in urinary pH that favours precipitation of calcium phosphate crystals and a metabolic acidosis that leads to hypercalciuria and hyperphosphaturia resulting from bone buffering, and hypocitraturia resulting from increased tubular reabsorption [4]. Alkaline citrates can be used to correct the metabolic acidosis, protect bone health and reduce risk of kidney stone formation [32,33]. Use of urinary pH as an assessment for dRTA is likely to be a more effective way to identify patients that require further investigation for dRTA than serum biochemistry [5]. Further studies to elucidate the utility of a single urinary pH measurement to screen for dRTA are required.

We assessed the utility of serum phosphate to predict hypercalciuria in stone-forming patients and demonstrated that hypophosphataemia was not associated with hypercalciuria; hypercalciuria was present in 55.2% of hypophosphataemic and 49.0% of normophosphataemic patients. In our dataset, 47.1% of all kidney stone patients enrolled into the biobank were hypercalciuric, in agreement with previous reports [34].

Kidney stone disease is commonly recurrent and at least 50% of patients who present with kidney stones will have another stone episode within 10 years of their first occurrence [35]. Recent studies have highlighted the importance of investigating those with recurrent stone disease for underlying monogenic metabolic disorders as these are reported to be present in >15% of those attending specialist kidney stone clinics [36–38]. Furthermore, this study replicates previous research demonstrating that potentially treatable metabolic abnormalities including hypercalciuria and hyperuricosuria are common in patients with nephrolithiasis. To make these diagnoses, a careful metabolic assessment including 24-h urine collection is required; we believe that a full metabolic assessment such as this should be undertaken in patients at high risk of future stone formation and in recurrent stone formers [4,5]. Current NICE guidelines note that effective treatments for hypercalciuria are available and that analysis of 24-h urine samples would enable identification of individuals with this phenotype. However, due to the paucity of evidence regarding the clinical and cost-effectiveness of a full metabolic evaluation, the committee were unable to make this a practice recommendation [6]. Research that aims to shed further light on the clinical and cost-effectiveness of 24-h urine collection in patients with kidney stones should be prioritized.

To our knowledge, this is the first study to assess the utility of blood tests as metabolic screening tools in unselected kidney stone patients. Our findings provide evidence in

support of the current NICE guidelines that recommend screening all individuals presenting with renal calculi with serum calcium measurement alone. Measurement of serum calcium levels has particular utility in detecting primary hyperparathyroidism in women who form kidney stones. This study demonstrates that assessing serum PTH, urate, chloride, bicarbonate and phosphate levels is of limited utility outside of a full metabolic assessment. We propose that the use of these blood tests as tools to screen for metabolic disorders should be discouraged as they are not cost-effective and may provide false reassurance that a metabolic abnormality is not present.

Acknowledgements

Sarah A. Howles is a National Institute for Health Research Academic Clinical Lecturer. We acknowledge the contribution to this study made by the Oxford Centre for Histopathology Research and the Oxford Radcliffe Biobank, which is supported by the National Institute for Health Research Oxford Biomedical Research Centre.

Conflicts of Interest

None declared.

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Abbreviations: dRTA, distal renal tubular acidosis; EAU, European Association of Urology; NICE, National Institute of Health and Care Excellence; PTH, parathyroid hormone.