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ORIGINAL PAPER

Stone recurrence among childhood kidney stone formers: results of a nationwide study in Iceland

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Abstract

Objectives To examine the stone recurrence rate among childhood kidney stone formers in the Icelandic population.

Materials and methods We retrospectively examined kidney stone recurrence in a recently reported population-based sample of 190 individuals who experienced their first stone before 18 years of age in the period 1985–2013. Of these 190 individuals, 112 (59%) were females and the median (range) age at the incident stone diagnosis was 15.0 (0.2–17.9) years. Stone recurrence was defined as an acute symptomatic episode with imaging confirmation or self-reported stone passage, new stone detected by imaging in asymptomatic patients, and suspected clinical stone episode without verification. The Kaplan–Meier method was used to assess stone-free survival and the Chi-square, Fisher's exact, Wilcoxon rank-sum and the log-rank tests to compare groups.

Results A total of 68 (35%) individuals experienced a second stone event, 1.7 (0.9–18.9) years after the initial diagnosis. The recurrence rate was 26%, 35%, 41% and 46% after 5, 10, 15 and 20 years of follow-up, respectively. The 5-year recurrence rate increased with time and was 9%, 24% and 37% in the periods 1985–1994, 1995–2004 and 2005–2013, respectively ($P=0.005$). No difference in stone recurrence was observed between the sexes ($P=0.23$).

Conclusions In our population-based sample of childhood kidney stone formers, the stone recurrence rate is similar to that reported for adults. The observed rise in stone recurrence with time may be related to closer patient follow-up in recent years or increased stone risk in general.

Keywords Nephrolithiasis · Urolithiasis · Epidemiology · Metabolic risk factors

Introduction

Kidney stone disease is a common disorder in adults with an estimated lifetime prevalence of 10–12% in men and 5–6% in women [1]. The epidemiology of stone disease in children and adolescents is much less well defined than in adults. Recent population-based studies from Iceland [2] and the US [3, 4] found an increasing incidence of pediatric stone disease, particularly in teenage girls.

The reported kidney stone recurrence rates in adults range from 30 to 50% within 5 years of the incident stone in untreated patients [5–9], but stone recurrence in individuals presenting in childhood has not been well characterized. Limited and mostly single-center data from previous childhood studies suggest a recurrence rate in the range of 20–70% over a follow-up period of 6–27 years [4, 6, 10, 11]. The reported kidney stone recurrence rates vary significantly between studies and are generally higher when the definition includes clinically suspected stone episodes without confirmation by imaging or stone visualization [12]. In light of the increasing incidence of pediatric kidney stone disease with its associated suffering and burden on the healthcare system [3], more studies of the clinical course of the stone disease in this young patient population are warranted.

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To accurately assess kidney stone recurrence, we conducted a retrospective study designed to identify virtually all known stone episodes in a nationwide sample of a recently reported group of Icelandic children and adolescents (aged < 18 years) with incident kidney stone disease.

Materials and methods

The study was approved by the National Bioethics Committee (NBC 03-002-S1-AG1) and the Icelandic Data Protection Authority. The principles of the Helsinki Declaration were followed in the clinical and research activities reported.

Study design and setting

We retrospectively examined kidney stone recurrence in a recently reported population-based sample of 190 individuals with idiopathic kidney stone disease who experienced their first stone before age 18 years in the period 1985–2013 [2]. Details of the patient search strategy and characterization of the cohort have previously been described [2, 13]. In brief, patients were initially identified by searching computerized databases at participating institutions for International Classification of Diseases (ICD) and radiology diagnosis codes and Nordic Classification of Surgical Procedures (NCSP) codes indicative of kidney stones during the years 1985–2013. For all patients identified by the search strategy, medical records were retrospectively reviewed for clinical stone episodes, documentation of self-reported stone passage and/or confirmation of kidney stone recurrence by imaging studies.

The children included in the study received care at the following institutions: Landspitali–The National University Hospital of Iceland in Reykjavik, a general hospital for approximately 75% of Iceland's population and a tertiary care center for the whole nation; Akureyri Hospital, a regional medical center in the Northern part of Iceland and the only hospital outside the Reykjavik area with a pediatric department; and Domus Radiology in Reykjavik, the largest privately run medical imaging clinic in the country. These institutions performed over 95% of all abdominal and urinary tract imaging studies in Iceland and close to 100% of surgical procedures for kidney stones during the study period.

Definition of stone recurrence

Kidney stone recurrence was defined as an acute symptomatic episode with imaging confirmation or self-reported passage of a stone, detection of a new stone by imaging in asymptomatic patients, or suspected clinical stone episode (flank or abdominal pain and hematuria) without verification.

Data acquisition

Medical records of the 190 childhood stone formers were reviewed for the presence of symptomatic and/or imaging manifestations of kidney stone recurrence. In addition, recurrent stone episodes were identified by the same strategy as was used to identify the incident kidney stone as described above, searching for ICD codes, radiology diagnosis codes and NCSP codes related to kidney stones. Clinical data abstracted from medical records, included sex, race, date and age at diagnosis, flank or abdominal pain, documentation of hematuria, self-reported stone passage, use of medications at diagnosis, comorbid diseases, prior history of kidney stones, date of all kidney stone episodes, height, weight, results of diagnostic urinary tract imaging, hospital admissions, stone removal procedures, and results of urinary metabolic risk factor evaluation. Follow-up time was defined as the time to first stone recurrence or the last date of follow-up which was June 1, 2014. If no evidence for stone recurrence was identified, an attempt was made to contact the legal guardians or the patients themselves (if they had turned 18 years) by phone, to inquire about stone episodes.

Anthropometric reference data, specific for sex and age, were used to establish baseline body mass index (BMI) percentiles and BMI *Z* scores based on height and weight, generated by equations provided by the United States Centers for Disease Control and Prevention [14, 15]. When height and weight measurements were not available within 6 months of the urine collection dates, these measures were extrapolated from data points on the individual patient growth charts, if acessible.

Urinary metabolic risk factor evaluation

To assess the prevalence of urinary metabolic risk factors for kidney stones at baseline (urine volume and pH and the urinary excretion of sodium, calcium, oxalate, uric acid, citrate, magnesium, cystine and the presence of 2,8-dihydroxyadenine crystals) [16–18], the results of the first available 24-h urine collection obtained within 3 years following the first kidney stone diagnosis were included in the study. If timed urine samples had not been collected, stone risk factor assessment was based on the first available random urine specimen obtained within 3 years of the first stone diagnosis, using solute-to-creatinine ratios to determine the prevalence of stone risk factors. Low urine volume, as a

risk factor for stone recurrence, was defined as urine output < 20 mL/kg/24 h [17].

Statistical analysis

Categorical data were expressed as numbers (%) and continuous data as median (range). The groups of patients with and without a recurrent stone episode were compared using Chi-square or Fisher's Exact tests and Wilcoxon rank-sum test. The Kaplan–Meier method was used to examine stone-free survival among all patients at risk, and the log-rank test was used to compare groups of patients stratified based on sex, time period of initial diagnosis, BMI percentiles and the presence of urinary metabolic risk factors. Individuals were censored at the time of death and at the end of follow-up (June 1, 2014). All statistics were calculated using STATA software, Intercooled STATA version 12.0 for MAC (Stata Corporation, College Station, Texas). Uncorrected *P* values of < 0.05 were used to determine statistical significance.

Results

Clinical characteristics

Of the 190 childhood stone formers, 112 (59%) were females and the median (range) age at the incident stone diagnosis was 15.0 (0.2–17.9) years. During a median follow-up time of 12.0 (0–29) years, 68 (36%) experienced stone recurrence, 1.7 (0.9–18.9) years following the incident stone. A flow diagram illustrating the documentation of stone recurrence is shown in Fig. 1. Of the 122 patients who had no evidence for recurrent stones in their medical records, 7 (6%) were deceased. Sixty-six (57%) of the 115 individuals alive were contacted by phone and screened for symptoms suggestive of a new stone, while 49 patients could not be reached. One of the 66 patients reported symptomatic kidney stone recurrence. A total of 34 patients experienced only a single kidney stone recurrence; 12 were found to have 2 recurrences; 10 had 3 recurrences; 4 had 4 recurrences, 5 experienced 5–9 recurrences each; and 3 patients suffered 10 or more recurrent stone episodes.

The majority of the individuals in this study had idiopathic kidney stone disease and were otherwise healthy and free of predisposing conditions. Important exceptions were 4 children with adenine phosphoribosyltransferase (APRT) deficiency, 1 child with cystinuria and 1 child with medullary sponge kidney and hypercalciuria. All these individuals had a documented recurrence except for one with APRT deficiency in whom allopurinol treatment was instituted immediately following the incident stone diagnosis.

The baseline characteristics of single and recurrent stone formers are shown in Table 1. There was no difference between the 2 groups with respect to sex, age at diagnosis, spontaneous stone passage or requirement for a stone removal procedure at first stone diagnosis, and the presence

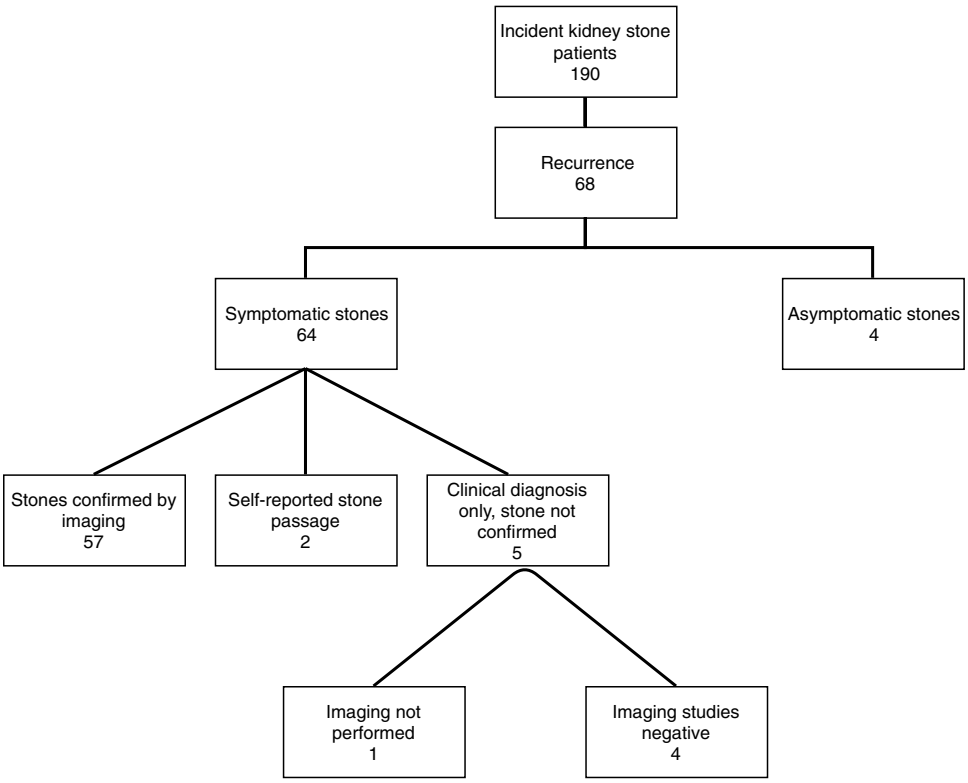

Fig. 1 Flow diagram of stone recurrence among incident patients with kidney stone disease

Table 1 Characteristics of single and recurrent kidney stone formers

	Single stone formers $n=122$	Recurrent stone formers $n=68$	*P* value
Male	54	24	0.23
Age (years)	15.0 (0.2–17.9) $n=122$	15.2 (0.7–17.8) $n=68$	0.72
BMI percentiles	48 (0–99) $n=45$	68 (4–99) $n=30$	0.04
Overweight[a]	7 (16)	10 (33)	0.07
Urinary tract anomalies (CACUT)	10 (8)	9 (13)	0.27
Other underlying conditions[b]	4 (3)	3 (4)	0.69
Number of stones present at initial diagnosis			
1	70 (58)	31 (46)	0.31
2	10 (8)	7 (10)	
≥3	10 (8)	12 (18)	
Unknown	12 (10)	6 (9)	
Stone not confirmed	20 (16)	12 (17)	
Stone diameter[c]			
1–5 mm	52 (43)	24 (35)	0.31
6–10 mm	28 (23)	13 (19)	
> 10 mm	6 (5)	9 (13)	
Unknown	16 (13)	10 (15)	
Stone not confirmed	20 (16)	12 (18)	
Stone location			
Kidney	39 (32)	27 (40)	0.66
Ureter	49 (40)	23 (34)	
Urinary bladder	2 (2)	2 (3)	
Unknown	12 (10)	4 (6)	
Stone not confirmed[d]	20 (16)	12 (17)	
Stone removal procedure at incident stone episode	43 (35)	31 (46)	0.16
ESWL	27	22	
Endoscopic removal	15	9	
Open surgery	3	5	

Data are presented as number (percentage) or median (range)

BMI body mass index, *ESWL* extracorporeal shockwave lithotripsy

[a]BMI ≥ 85th percentile for age and sex

[b]Other underlying conditions included spinal muscular atrophy, cerebral palsy, osteogenesis imperfecta, Duchenne muscular dystrophy and neuronal ceroid lipofuscinosis

[c]Largest stone, if more than one detected by imaging

[d]Imaging performed, stones not detected

of congenital malformations of the kidney and urinary tract or comorbid conditions. Information on BMI was only available for 75 children, of whom 45 were single stone formers and 30 with recurrent stones. The median BMI percentile at first kidney stone diagnosis was significantly lower among the single stone formers, 48th percentile compared with 68th percentile in those with recurrent disease ($P=0.04$). When 2 sarcopenic children with underlying neurological disorders were excluded from the BMI calculations, the significance of this difference became borderline ($P=0.06$). Ten (33%) recurrent stone formers were overweight compared with 7 (16%) single stone formers ($P=0.07$). No significant difference was noted between single and recurrent stone formers regarding the number of stones present at first diagnosis and the size, location or spontaneous passage of the incident stone (Table 1).

Kidney stone recurrence

A Kaplan–Meier survival plot depicting stone-free survival for all the 190 first-time kidney stone formers is shown in Fig. 2. Recurrence was observed in approximately 13% at

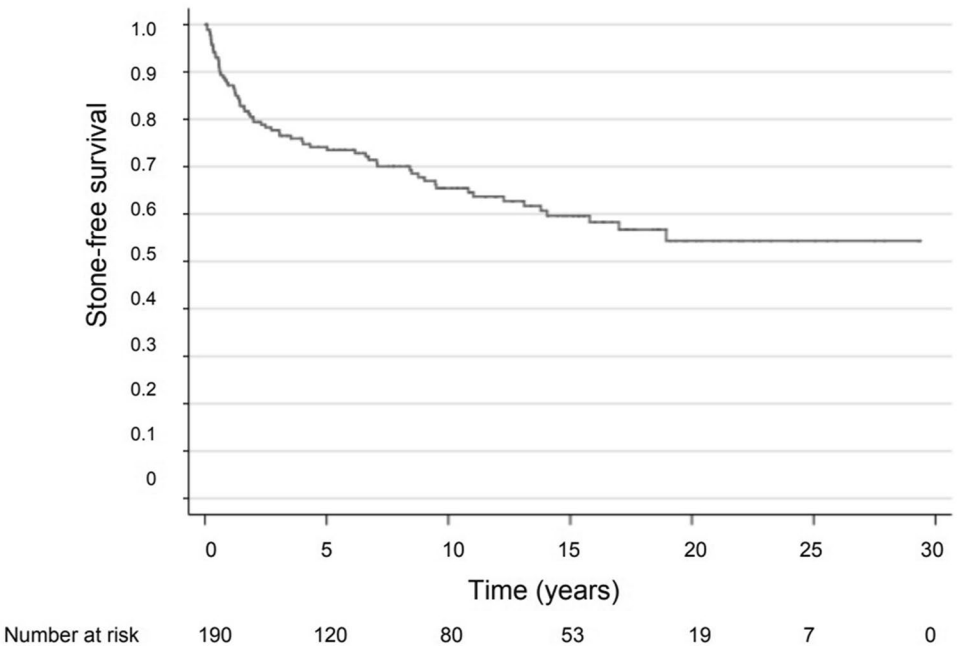

Fig. 2 Stone-free survival (proportion) of all incident kidney stone patients in the years 1985–2013. Kaplan–Meier method

one year, 22% at 3 years, 26% at 5 years, 35% at 10 years, 41% at 15 years and 46% at 20 years. When the stone-free survival analysis was limited to the 63 patients with confirmed stone recurrence, the rate was 11% at one year, 18% at 3 years, 22% at 5 years, 32% at 10 years, 39% at 15 years and 44% at 20 years. No difference in stone recurrence was observed between the sexes ($P=0.23$; Fig. 3a), nor between those below and above the age of 13 years at diagnosis of kidney stone disease ($P=0.62$). The recurrence rate varied significantly with the year of diagnosis; at 5 years it was 9% for patients diagnosed in the years 1985–1994, 24% for those diagnosed in 1995–2004 and 37% when the diagnosis had been made in 2005–2013 ($P=0.005$; Fig. 3b). A difference in stone recurrence of borderline significance ($P=0.05$) was seen for those with a BMI percentile below and above the median of our cohort (Fig. 3c). Among the 93 patients who had urinary metabolic risk factor data available, the stone recurrence rate was significantly higher in those with at least one such risk factor identified ($P=0.03$; Fig. 3d).

Urinary metabolic risk factor evaluation

Table 2 demonstrates the results of metabolic risk factor assessment which was available for 93 (49%) patients within 3 years of diagnosis. Of those, 66 had collected 24-h urine samples at 0.3 (0–2.7) years after the incident stone, while 27 had only returned random void urine specimens. One or more metabolic risk factors were identified in 79 (85%) children, of which hypomagnesuria and hypocitraturia were most commonly noted. Forty-five (68%) of the 66 children who had collected 24-h urine samples had low urine volume. Among the recurrent stone formers, 45 (66%) underwent metabolic risk factor testing, compared with 48 (39%) of the single stone formers ($P<0.001$). No significant difference in the presence ($P=0.08$) or number ($P=0.16$) of risk factors between the two groups was observed. The recurrent stone formers, however, had a significantly lower 24-h urinary magnesium excretion ($P=0.03$), and patients with urinary magnesium excretion above the median had a significantly lower stone recurrence rate ($P=0.04$). The 24-h urinary calcium excretion did not differ between the groups, whereas in the small subset of patients with only single-void urine samples available, the calcium-to-creatinine ratio was significantly higher in the children who experienced at least one stone recurrence. No significant differences were observed for other urinary risk factors.

Discussion

In this nationwide study, approximately one-quarter of childhood kidney stone formers experienced a stone recurrence at 5 years and 46% at 20 years following the initial stone diagnosis. Stone recurrence was not associated with sex or age at first diagnosis. Interestingly, recurrent stone formers tended to have higher measures of body mass compared with single stone formers, and patients diagnosed in recent years had a greater recurrence rate than those presenting early in the study period.

The current investigation is the first published nationwide study on kidney stone recurrence in childhood stone formers. A recent single-center study in the US, carried out by Tasian et al. at the Children's Hospital of Philadelphia, examined the 3-year kidney stone recurrence in children

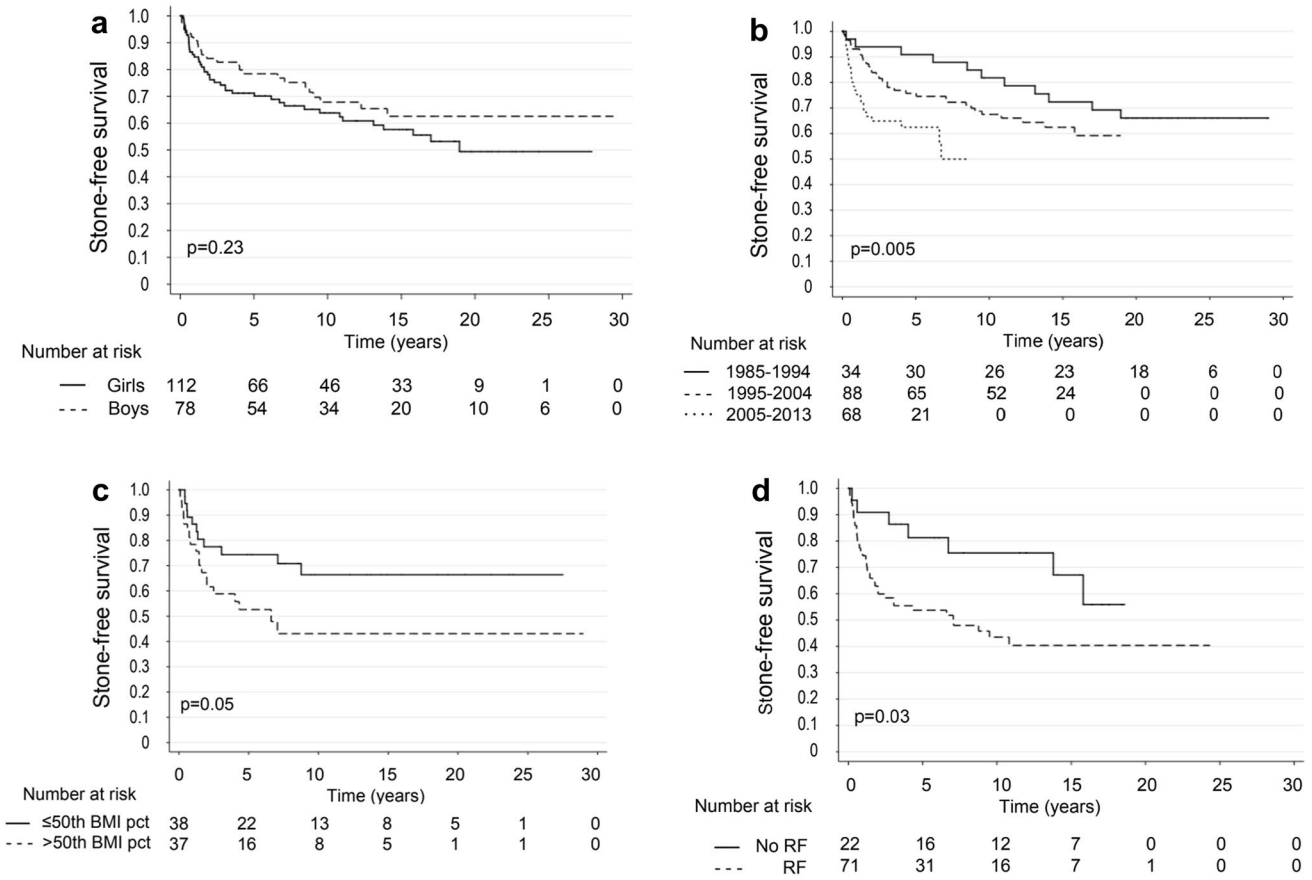

Fig. 3 Stone-free survival (proportion) by **a** sex, **b** year of initial kidney stone disease diagnosis, **c** BMI percentiles above and below the median, and **d** presence of urinary metabolic risk factors (RF). Kaplan–Meier method. Groups were compared using the log-rank test

aged 3–18 years with incident symptomatic stone disease [10]. The investigators observed recurrent stones in approximately 50% of cases compared to a 3-year overall and confirmed recurrence rates of 22 and 17%, respectively, in the present study. As in our study, almost all stone recurrence was symptomatic. The definition of stone recurrence in the US study was limited to episodes of flank pain or vomiting associated with radiographic signs of a new concrement after confirming clearance of the first stone. Although the less strict definition of stone recurrence in the present study would be expected to yield a higher recurrence rate, the use of more selected patient sample may have contributed to the greater stone recurrence observed in the US study, a single-center investigation from a large referral institution. This notion is supported by published studies requiring confirmation of a stone by report of stone passage or imaging, which have generally reported lower recurrence rates than studies that have included unconfirmed clinically suspected stone episodes [12]. Another recent study from the US, examining a large population-based cohort and focusing primarily on the incidence of kidney stones in children below 18 years of age, showed an overall recurrence rate of 44% at 25 years [4], which is similar to our findings. Notably, the stone recurrence rate observed in our study appears to be similar to what has been reported in adults [5, 7–9, 19]. The 5-year recurrence rate in our study increased significantly with the year of diagnosis of the first kidney stone and was by far highest late in the study period. No single study has examined time trends in stone recurrence. The recurrence rate observed in two pediatric studies [6, 11] published around 1990 ranged from 20 to 70% after 10 years and 27 years of follow-up, respectively, whereas the rate was 50% after 3 years in the more recent US study by Tasian et al. [10]. Indeed, in the current study the recurrence rate in those diagnosed in 2005–2013 was roughly 40% at 3–5 years and almost 50% at the end of follow-up, which is similar to the results of the aforementioned US study carried out during the years 2008–2014 [10]. While the increase in stone recurrence with the year of diagnosis likely is linked to the parallel increase in the incidence of kidney stone disease [2], it may also partly be explained by increasing awareness of pediatric kidney stone disease and a more meticulous follow-up of the stone-forming population. As previously reported by our group [2], the use of CT scanning for the diagnosis

Table 2 Comparison of urinary metabolic risk factors among single and recurrent stone formers

	Single stone formers $n=122$	Recurrent stone formers $n=68$	*P* value
Patients evaluated	48 (39)	45 (66)	< 0.001
Risk factor present	33 (69)	38 (84)	0.08
Number of risk factors	2 (0–4)	2 (0–4)	0.16
24-h urine collection			
Volume (mL/kg)	14.89 (5.21–40.28) $n=30$	15.73 (5.52–38.89) $n=36$	0.82
pH	6.00 (4.85–7.00) $n=21$	6.00 (5.20–6.50) $n=28$	0.96
Calcium (mmol/kg)	0.07 (0.02–0.15) $n=30$	0.06 (0.01–0.27) $n=34$	0.77
Magnesium (mmol/1.73 m^2)	2.39 (0.13–6.06) $n=25$	1.47 (0.33–9.95) $n=32$	0.025
Oxalate (mmol/1.73 m^2)	0.18 (0.05–0.31) $n=27$	0.15 (0.05–0.41) $n=30$	0.26
Uric acid (mmol/kg)	0.05 (0.00–0.09) $n=29$	0.05 (0.01–0.11) $n=33$	0.28
Citrate (mmol/1.73 m^2)	0.83 (0.00–2.72) $n=18$	0.78 (0.00–2.12) $n=26$	0.63
Sodium (mmol/kg)	1.98 (0.60–7.05) $n=28$	1.99 (0.80–7.43) $n=35$	0.85
Random urine samples (solute-to-creatinine ratio in mmol/mmol)			
Calcium	0.42 (0.02–1.09) $n=18$	1.03 (0.09–2.84) $n=10$	0.02
Magnesium	0.57 (0.25–1.11) $n=4$	0.51 $n=1$	1.00
Oxalate	0.03 (0.02–0.07) $n=6$	0.03 (0.01–0.11) $n=7$	1.00
Uric acid	0.44 (0.22–1.48) $n=4$	0.26 (0.12–1.91) $n=3$	0.72
Citrate	0.09 (0.04–0.38) $n=4$	0.33 (0.17–0.48) $n=2$	0.16

Data are presented as number (percentage) or median (range)

of childhood stone disease increased markedly during the study period. These results suggest that some of the upsurge in stone recurrence observed in our study may in fact be explained by a more frequent use of highly sensitive imaging techniques such as CT.

In line with the findings of previous studies, the majority of the individuals tested had at least one urinary metabolic kidney stone risk factor identified [20, 21]. Overall, we did not find a significant difference in the number of risk factors between single and recurrent stone formers. However, individuals with at least one established stone risk factor experienced their first recurrence significantly earlier. Prior studies have demonstrated a higher rate of recurrence in childhood stone formers with either the presence or a greater number of documented urinary metabolic risk factors [21, 22]. In particular, abnormal urine levels of calcium and citrate and higher urinary calcium excretion have been more commonly observed among recurrent stone formers than single stone formers [22, 23]. The 24-h urinary calcium excretion did not differ between single and recurrent stone formers in the present study. To the contrary, the random void urinary calcium-to-creatinine ratio in a subset of patients who had not collected 24-h urine samples was significantly higher in the children with at least one stone recurrence. This discrepancy may be caused by methodological shortcomings, including small sample size. Our study also failed to show a signficant difference in urinary citrate excretion between the single and recurrent stone formers. By contrast, patients with recurrent stones had a significantly lower urinary magnesium excretion than single stone formers. We could only identify one other study in which low urinary magnesium excretion was associated with higher stone risk in children [24], but hypomagnesuria might be a risk factor for stone formation in youth. The potential role of magnesium in kidney stone disease is further supported by results of a genome-wide association study in the Icelandic population showing an association of a sequence variant (rs199565725[delAC]) in the *CLDN14* gene, whose product is a member of the claudin

superfamily of proteins that regulate paracellular transport of cations at epithelial tight junctions in the thick ascending limb, with both kidney stones and increased serum magnesium levels [25]. It should be noted, however, that owing to the retrospective nature of our study, data on metabolic risk factors were lacking for approximately half of the participants, and most of the remaining ones had only a single urine sample or collection available. This shortcoming limits the conclusions that can be drawn from the urinary metabolic risk factor findings in our study population. Current guidelines recommend the analysis of two consecutive 24-h urine collections for metabolic risk factor evaluation in children and other high-risk patients following the first kidney stone diagnosis [26].

Interestingly, we observed a significant increase in stone recurrence with higher measures of body mass. Previous studies in adults have clearly demonstrated an association of higher BMI with increased risk of incident calcium oxalate stones [27, 28]. In children and adolescents, however, epidemiologic data do not suggest a link between higher BMI percentiles and stone formation [29]. Indeed, childhood stone formers have been found to have a slightly lower BMI percentile than non-stone-forming individuals in the general population [29, 30], whereas studies of the association between obesity and urinary metabolic risk factors for stone formation in children have shown conflicting results [31, 32].

The main strength of our study is the nationwide population-based design with the inclusion of practically all children and adolescents diagnosed with kidney stones in Iceland during the study period. The fact that single stone formers with no evidence for stone recurrence in their medical record were contacted at the end of the study period, and screened for symptoms suggestive of stone recurrence, adds further strength to the study. Nevertheless, we may have missed patients with short-lived symptoms who did not seek medical care.

The main limitations of this work are the retrospective design and small sample size, hampering the statistical analyses. Furthermore, insufficient data were available on several important factors, such as height, weight and the results of urinary metabolic risk factor analysis. The data on urinary metabolic risk factors were particularly scarce during the first 15 years of the study period, resulting in an incomplete dataset overall. In addition, only a single metabolic risk factor assessment was performed in each case, further restricting the conclusions that can be drawn from the findings. Finally, although the vast majority of recurrences were symptomatic, incomplete documentation in the medical records or limited use of imaging studies in the early years of the study may have negatively impacted the identification of kidney stone recurrence.

Conclusions

The recurrence rate of nephrolithiasis among childhood kidney stone formers in the Icelandic population is high and similar to that reported in adults. Stone recurrence was not affected by sex or age at first stone diagnosis, while our findings suggest an increase in the recurrence rate in recent years with a preponderance in individuals with a greater body mass. Prospective studies using a uniform and generally accepted definitions of kidney stone recurrence are needed. Finally, the potential contribution of lifestyle and environmental factors to the observed increase in kidney stone recurrence warrants further study.

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Compliance with ethical standards

Conflict of interest None of the authors declared financial or other conflicting interests. No honorarium, grant, or any other form of payment was given to anyone to produce the manuscript. The study sponsor had no role in study design; the collection, analysis, and interpretation of data; the writing of the report and the decision to submit the manuscript for publication.

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