Pediatric Nephrology (2018) 33:1375–1384
https://doi.org/10.1007/s00467-018-3947-x

ORIGINAL ARTICLE

Incidence of kidney stone disease in Icelandic children and adolescents from 1985 to 2013: results of a nationwide study

Vidar O. Edvardsson [1,2] · Solborg E. Ingvarsdottir [1,2] · Runolfur Palsson [1,3] · Olafur S. Indridason [3]

Received: 27 December 2017 / Revised: 19 March 2018 / Accepted: 20 March 2018 / Published online: 6 April 2018

Abstract

Background An increase in the incidence of kidney stone disease has been reported for all age groups worldwide. To examine this trend, we conducted a nationwide study of the epidemiology of kidney stones in Icelandic children and adolescents over a 30-year period.

Methods Computerized databases of all major hospitals and medical imaging centers in Iceland were searched for International Classification of Diseases and radiologic and surgical procedure codes indicative of kidney stones in patients aged < 18 years, followed by a thorough medical record review. Age-adjusted incidence was calculated for the time intervals 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2013. Time trends in stone incidence were assessed by Poisson regression. The prevalence of stone disease for the years 1999–2013 was also determined.

Results Almost all the 190 patients (97%) that we identified had symptomatic stones, and acute flank or abdominal pain and hematuria were the most common presenting features. The total annual incidence of kidney stones increased from 3.7/100,000 in the first 5-year interval to 11.0/100,000 during the years 1995–2004 ($p < 0.001$) and decreased thereafter to 8.7/100,000 in 2010–2013 ($p = 0.63$). The incidence rise was highest in girls aged 13–17 years, in whom it rose from 9.8/100,000 in 1985–1989 to 39.2/100,000 in 2010–2013 ($p < 0.001$), resulting in an overall female predominance in this age group. The mean annual prevalence of stone disease in 1999–2013 was 48/100,000 for boys and 52/100,000 for girls.

Conclusion We found a significant increase in the incidence of childhood kidney stone disease, driven by a dramatic increase of stone frequency in teenage females which is poorly understood and warrants further study.

Keywords Kidney stones · Nephrolithiasis · Urolithiasis · Epidemiology

Introduction

Kidney stone disease is a common health problem with an estimated lifetime prevalence of approximately 10–12% in men and 5–6% in women [1, 2]. Several recent studies in the adult population have described a significant rise in the incidence and prevalence of symptomatic kidney stones over the last two or three decades [1, 3–6]. Interestingly, a study recently published by our group showed a significant increase in the incidence of symptomatic stones in the age group 18–29 years in both sexes, in whom the rate of symptomatic stones rose significantly faster in women than that in men [3]. Although the epidemiology of kidney stone disease in children and adolescents is less well defined than in adults, several reports suggest a significant increase in the incidence of kidney stones in children [7–9] and a number of studies have shown a more pronounced rise in girls than boys [7, 10, 11]. Thus, kidney stones may be becoming more common in young females. Importantly, significant morbidity and healthcare cost are associated with kidney stone disease at any age [12, 13].

A number of well-defined clinical factors are known to increase the risk of calcium kidney stone disease. Urinary metabolic risk factors, which include idiopathic hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, and low urine volume[14–16], have been reported in 40–95% of first-time pediatric stone formers [15, 17, 18]. There is evidence that alterations in the prevalence of these risk factors may be partially responsible for the epidemiological changes observed [19]. Finally, various rare inherited

✉ Vidar O. Edvardsson
vidare@landspitali.is

[1] Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland

[2] Children's Medical Center, Landspitali–The National University Hospital of Iceland, 101 Reykjavik, Iceland

[3] Division of Nephrology, Internal Medicine Services, Landspitali–The National University Hospital of Iceland, Reykjavik, Iceland

disorders and urinary tract anomalies are important but frequently overlooked causes of urinary tract stone disease in children [20, 21]. Thus, improved understanding of the epidemiology of stone disease in childhood and adolescence is important.

In order to accurately assess time trends in the incidence and prevalence of kidney stone disease in children and adolescents, we conducted a retrospective study designed to identify all known childhood cases of kidney stones in Iceland during the last three decades. We also examined the presence of known risk factors for kidney stone formation.

Methods

Study design and setting

A retrospective, nationwide study of children and adolescents aged < 18 years, who were diagnosed with kidney stones in Iceland during the period 1985–2013, was conducted. Participating institutions included the Children's Medical Center at Landspitali–The National University Hospital of Iceland in Reykjavik, which serves as a general hospital for more than half of the country's population and a tertiary care center for the whole nation; Akureyri Hospital in the northern part of Iceland which is the only hospital outside the Reykjavik area with a pediatric department; and Domus Radiology in Reykjavik, a privately operated medical imaging clinic. These institutions performed over 95% of all abdominal and urinary tract imaging studies and all pediatric surgical procedures for kidney stone disease in Iceland during the study period.

Patient search strategy

Patients were identified by searching computerized databases at participating institutions for International Classification of Diseases (ICD) and radiology diagnosis codes and surgical procedure codes indicative of kidney stones. Although electronic recording of diagnostic codes was introduced in 1983, patients who had their first documented kidney stone event before 1985 were excluded from the incidence analysis due to incomplete electronic coding of health records during 1983 and 1984. The search strategy has previously been successfully used for the study of adult kidney stone disease in Iceland [3] and included the following codes:

1. *ICD diagnosis codes*: ICD-9 codes 592.0, 592.1, 592.9, 270.0, 271.8, and 788.0. ICD-10 codes N20.0, N20.1, N20.2, N20.9, N21.0, N21.1, N21.8, N21.9, N22.0, N22.8, N23, E72.0, E74.8, and E79.8.
2. *Radiology diagnosis codes*: 460.812, 501.812, 510.812, 940.812, 950.812, 840.812, and 850.812.
3. *NOMESCO Classification of Surgical Procedures (NCSP) codes*: KAE00, KAE01, KAE10, KAE11, KAE12, KAE96, KAE97, KAE98, KBE00, KBE01, KBE12, KBE22, KBE96, KBE97 KBE98, KCE00, KCE01, KCE02, KAT00, KBT00, and KCT00.

Characterization of study subjects

A retrospective chart review was conducted for all patients identified by our search strategy to confirm the diagnosis of kidney stone disease. Data obtained from medical records included sex, race, and date and age at diagnosis; prior history of stones; congenital anomalies of the kidney and urinary tract; severe neuromuscular disorders and other conditions leading to immobility; use of drugs that are known to predispose to stone formation; height and weight; clinical manifestations associated with kidney stones; the detection of stones by medical imaging procedures; patient-reported stone passage; and results of urinalysis, urine cultures, and kidney stone analysis. Symptomatic stone events were defined as either acute flank or abdominal pain associated with hematuria and/or the detection of stones by a medical imaging study, or a patient-reported stone passage. Patients with stones confirmed by imaging and a simultaneous urinary tract infection were classified as symptomatic, even if they had no other complaints suggestive of nephrolithiasis.

Results of the first available 24-h urine collection, obtained within 3 years of the incident stone diagnosis, were used to assess the prevalence of urinary metabolic risk factors for stone formation. When the first two urine collections had been obtained during the same week, results from both samples were used and the more extreme solute values (higher values for promoters and lower values for inhibitors of stone formation) and the average of the pH of the two collections were included. When timed urine samples were not available, urinary risk factor assessment was based on the first randomly voided urine specimen obtained within 3 years of the incident stone. Results of the urinary metabolic risk factor evaluation were expressed as the amount of solute excreted in 24 h, adjusted for body size (timed collections), or solute-to-creatinine ratios (random urine samples). Timed urine collections were considered sufficient if the creatinine excretion was in the range of 133–222 μmol/kg/24 h (15–25 mg/kg/24 h). Previously published reference data for urine pH and urinary excretion of solutes were used to identify abnormal values [22]. Low urine volume, as a risk factor for a first kidney stone was defined as less than 1.0 mL/kg/h in younger children [23–25] and 1000 mL/24 h in older children and adolescents who weighed 40 kg or more [26, 27]. Pediatric anthropometric reference data, specific for age and sex, were used to establish percentiles for weight and body mass index (BMI) [28], and BMI *Z* scores were generated from equations provided by the

US Centers for Disease Control and Prevention [28, 29]. When measurements of height and weight were not available within 6 months of the dates of urine collections, this information was extrapolated from data points in the respective patient growth charts, if available.

Statistical methods

Incidence and prevalence of kidney stone disease were calculated based on the total population of Iceland aged 0–17 years, which numbered 79,758 at the end of the study period (December 31, 2013; www.statice.is/Statistics/Population/Overview). Both the crude incidence and the incidence stratified by age and sex were calculated. Poisson regression analysis was used to assess time trends in kidney stone incidence, using the incidence rate in each year of the study for the whole patient sample, for each sex and the 2 age groups, < 13 and ≥ 13 years. The Poisson regression was performed for the whole study period and separately for the first and second half. To simplify the presentation of the data, the average incidence was calculated for the time intervals1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2013. Annual prevalence was calculated only for the years 1999–2013 because single stone formers diagnosed prior to 1983 might have been missed in the early years of the study period. Groups were compared using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. The statistical analysis was performed using STATA software, intercooled STATA version 12.0 for MAC (Stata Corporation, College Station, TX).

Results

The search strategy identified 251 individuals < 18 years of age, with ICD and/or radiology diagnosis codes or surgical procedure codes suggestive of kidney stone disease. Most of the children were detected by more than one of the three coding systems. Following chart review, 37 patients who did not have kidney stones (the majority had abdominal calcifications other than kidney stones and a few cases had been assigned an erroneous code) were excluded from the study. Twenty-four patients who carried a diagnosis of kidney stone disease prior to the year 1985 were also excluded.

Clinical characteristics of the patients are presented in Table 1. The number of incident kidney stone formers was 190, of whom 112 (59%) were girls. Sixty-one (32%) were < 13 years of age, 29 (48%) of whom were girls, and 129 (68%) were ≥ 13 years, including 83 (64%) girls. The children were exclusively non-Hispanic Whites, reflecting the ethnic composition of the Icelandic population. A total of 108 (57%) children required hospital admission for pain control and/or emergency surgical management. The median BMI was close to the average value of the reference population, except for boys aged ≥ 13 years in whom the observed median BMI approached the 80th percentile (Table 1). The majority of the individuals had idiopathic calcium stone disease and were otherwise healthy and free of predisposing conditions. Exceptions were four children with adenine phosphoribosyltransferase (APRT) deficiency and one child with medullary sponge kidney and hypercalciuria. Seven (4%) children had other underlying disorders predisposing to kidney stone formation, including spinal muscular atrophy ($n = 2$), cerebral palsy ($n = 2$), osteogenesis imperfecta ($n = 1$), Duchenne muscular dystrophy ($n = 1$), and neuronal ceroid lipofuscinosis with epilepsy treated with topiramate ($n = 1$). In addition, 19 (10%) children had 21 structural malformations of the urinary tract, i.e. vesicoureteral reflux ($n = 9$), ureteropelvic junction stenosis ($n = 5$), ureterovesical junction stenosis ($n = 1$), incomplete ureteral duplication on the stone forming side ($n = 2$), bladder exstrophy ($n = 1$), mild to moderate posterior urethral valves with normal kidney function ($n = 1$), and hypospadias ($n = 2$).

The incident kidney stone was symptomatic in 185 (97%) patients. The most common clinical features were flank or abdominal pain in 158 (85%), followed by hematuria in 135 (73%), and 8 (4%) had concurrent urinary tract infection. Flank pain was a less frequent complaint in the younger children ($p < 0.001$), while hematuria appeared equally often in both age groups (Table 1). Of the 158 stones confirmed by imaging, 138 (87%) were located in the kidneys or ureters (Table 1). Spontaneous stone passage was observed in 116 (61%) patients, 67 girls and 49 boys. Eighty percent ($n = 61$), 20% ($n = 8$), and 13% ($n = 2$) of stones that were 1–5, 6–10, and > 10 mm in the largest diameter, respectively, were passed spontaneously. The spontaneous stone passage rate was significantly lower in children aged < 13 years compared with those aged ≥ 13 years, 46 versus 68% ($p = 0.002$). The presence of more than 1 stone at the time of diagnosis was confirmed in 39 (21%) patients (Table 1).

Overall, the annual incidence of kidney stones increased significantly over the study period. The incidence rate rose from 3.7/100,000 in the first 5-year period to 11.0/100,000 during the years 1995–2004 ($p < 0.001$), but thereafter decreased slightly to 8.7/100,000 in 2010–2013 ($p = 0.63$). Figure 1 shows the incidence in girls which rose significantly from 2.7/100,000 in 1985–1989 to 14.2/100,000 in the years 1995–1999 ($p < 0.001$), but remained relatively stable thereafter and was 14.2/100,000 at the end of the study period ($p = 0.16$). The incidence rise in girls was primarily driven by a large increase in the age group 13–17 years, for whom the rate increased from 9.8/100,000 in 1985–1989 to 39.2/100,000 in 2010–2013 ($p = 0.001$). The incidence in girls < 13 years of age at diagnosis increased significantly from 0/100,000 during the first 5 years of the study period to 7.2/100,000 in 1995–2000

Table 1 Clinical characteristics at initial diagnosis of kidney stone disease

	Boys		Girls	
	< 13 years *n* = 32	≥ 13 years *n* = 46	< 13 years *n* = 29	≥ 13 years *n* = 83
Age, years	8.1 (5.2–11.1)	16.4 (15.0–17.4)	9.4 (7.1–10.9)	16.4 (14.9–17.3)
BMI percentile	50 (31–59) *n* = 17	82 (39–95) *n* = 12	39 (12–77) *n* = 20	52 (36–78) *n* = 26
Urinary tract malformations	6	3	3	7
Other underlying conditions	3	3	1	0
Presenting features				
Flank pain	20	41	21	76
Hematuria	24	35	17	59
UTI	1	0	4	3
Other/unclear	1	1	1	2
Asymptomatic	1	2	1	1
Number of stones				
1	14	24	15	48
2	4	4	4	5
≥ 3	5	4	7	6
Unknown	5	4	1	8
Stone not visualized	4	10	2	16
Stone diameter*				
1–5 mm	8	22	9	37
6–10 mm	10	8	11	12
> 10 mm	3	2	3	7
Unknown	7	4	4	11
Stone not visualized	4	10	2	16
Stone location*				
Kidney	10	15	18	23
Ureter	10	17	8	37
Urinary bladder	3	0	0	1
Unknown location	5	4	1	6
Stone not visualized	4	10	2	16
Spontaneous stone passage	16	33	12	55
Stone removal procedures	16	13	17	28
ESWL	12	5	13	19
Endoscopic	4	4	4	12
Open surgery	2	4	1	1

Data are presented as number (*n*) or median (interquartile range). Other underlying conditions include spinal muscular atrophy, cerebral palsy, osteogenesis imperfecta, Duchenne muscular dystrophy, and neuronal ceroid lipofuscinosis

BMI body mass index, *ESWL* extracorporeal shockwave lithotripsy, *UTI* urinary tract infection

*Largest stone if more than one stone detected

($p = 0.002$), but subsequently decreased to 4.4/100,000 in 2010–2013 ($p = 0.24$). In boys (Fig. 2), the overall change in incidence was not statistically significant ($p = 0.39$). The incidence was 4.7/100,000 at the beginning of the study period, increased to 11.0/100,000 during 2000–2004 ($p = 0.07$), and decreased to 4.3/100,000 in 2010–2013 ($p = 0.02$ for the decrease from year 2000). The incidence in boys diagnosed before the age of 13 years increased from 0.7/100,000 in 1985–1989 to 8.2/100,000 in 2000–2004 ($p = 0.21$), but decreased thereafter to 2.5/100,000 in 2010–2013 ($p = 0.04$). The incidence among boys diagnosed after their 13th birthday did not change significantly.

The mean annual prevalence of kidney stone disease during the years 1999–2013 was 48/100,000 for boys

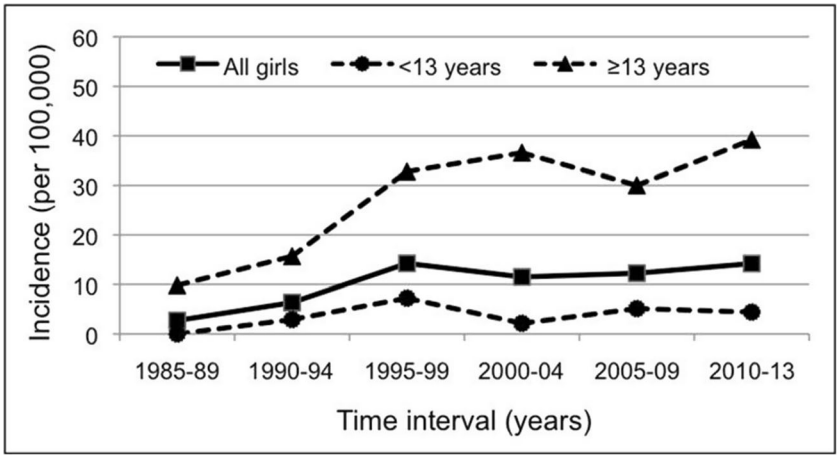

Fig. 1 Mean annual incidence of kidney stone disease in girls, from 1985 to 2013

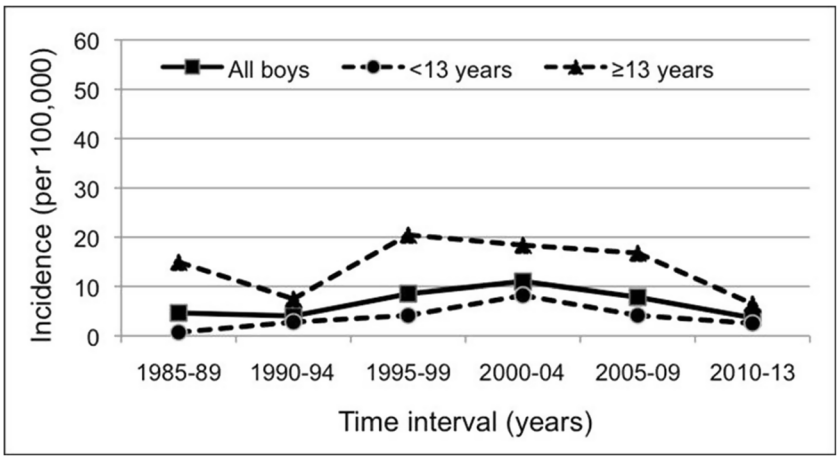

Fig. 2 Mean annual incidence of kidney stone disease in boys, from 1985 to 2013

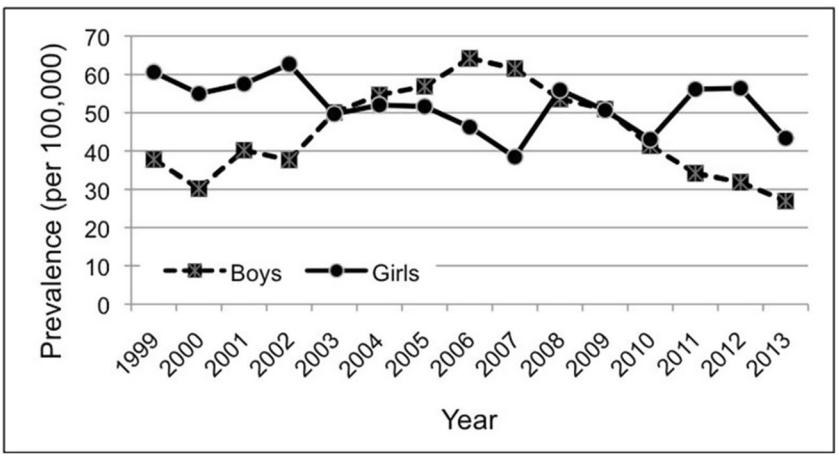

Fig. 3 Annual prevalence of kidney stone disease in boys and girls, from 1999 to 2013

and 52/100,000 for girls (Fig. 3). Trends in the use of diagnostic imaging during the study period are presented in Fig. 4. The use of intravenous pyelography (IVP) for the diagnosis of stone disease increased sharply in the years 1990–2004, when most of the rise in stone incidence was observed. Later in the study period, the use of computed tomography (CT) increased, whereas a significant reduction in the use of IVP and other imaging modalities was observed.

Urinary metabolic risk factor analysis by sex and age at diagnosis is displayed in Tables 2 and 3. Urinary metabolic risk factor analysis was available for 93 children within 3 years of the diagnosis. Of these, 66 had collected 24-h urine samples at 0.3 (0.1–0.66) years following the

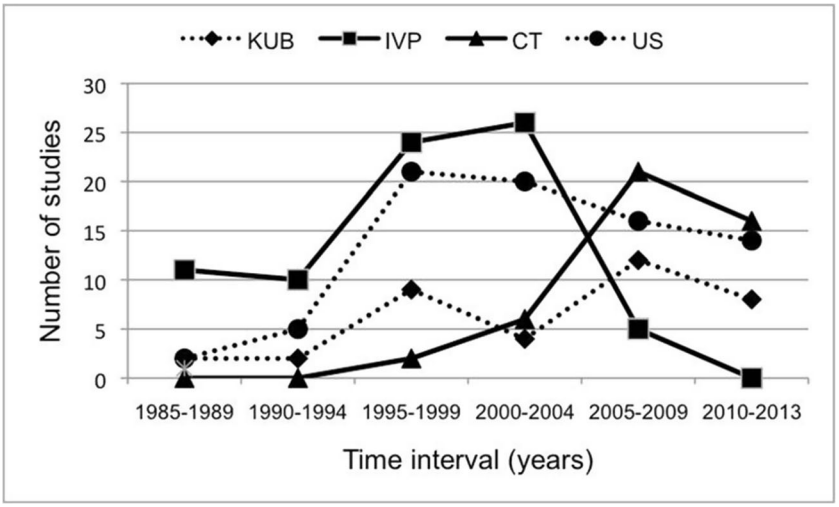

Fig. 4 Medical imaging studies leading to kidney stone diagnosis throughout the study period (*CT* computed tomography, *IVP* intravenous pyelography, *KUB* kidney ureter bladder plain x-ray, *US* renal ultrasound)

Table 2 Analysis of urinary metabolic risk factors for kidney stones in boys and girls

	Boys ($n = 78$)	Girls ($n = 112$)	p value
Patients evaluated	37 (47)	56 (50)	0.73
Risk factor present	28 (76)	43 (77)	0.90
Number of risk factors	2 (2–2)	2 (1–2)	0.64
24h urinary excretion			
Urine volume (mL/kg)	18.87 (16.27–29.05) $n = 23$	14.03 (9.72–22.82) $n = 43$	0.01
Low urine volume	9 (40)	30 (70)	0.02
Urine pH	6.0 (5.5–6.5) $n = 17$	6.0 (5.6–6.4) $n = 32$	0.97
Calcium (mmol/kg)	0.07 (0.06–0.10) $n = 22$	0.06 (0.04–0.09) $n = 42$	0.18
Magnesium (mmol/1.73 m^2)	2.53 (1.50–3.30) $n = 19$	1.57 (1.18–2.39) $n = 38$	0.04
Oxalate (mmol/1.73 m^2)	0.18 (0.15–0.29) $n = 19$	0.15 (0.10–0.19) $n = 38$	0.03
Uric acid (mmol/kg)	0.05 (0.05–0.07) $n = 22$	0.05 (0.03–0.06) $n = 40$	0.04
Citrate (mmol/1.73 m^2)	0.74 (0.41–0.98) $n = 13$	0.84 (0.16–1.24) $n = 31$	0.75
Sodium (mmol/kg)	2.16 (1.67–3.43) $n = 22$	1.84 (1.35–2.61) $n = 41$	0.06
Creatinine (mmol/kg)	0.17 (0.14–0.20) $n = 21$	0.15 (0.12–0.18) $n = 35$	0.08
Solute-to-creatinine ratio in randomly voided urine samples			
Calcium	0.57 (0.35–0.74) $n = 15$	0.48 (0.17–1.00) $n = 13$	0.73
Magnesium	0.51 (0.45–0.69) $n = 5$	NA	–
Oxalate	0.04 (0.02–0.06) $n = 8$	0.02 (0.02–0.05) $n = 5$	0.67
Uric acid	0.59 (0.28–1.48) $n = 5$	0.17 (0.12–0.22) $n = 2$	0.05
Citrate	0.09 (0.06–0.24) $n = 4$	0.33 (0.17–0.48) $n = 2$	0.16
Creatinine	5.00 (2.50–9.03) $n = 15$	6.20 (3.20–12.00) $n = 13$	0.66

Data are presented as number (percentage) and median (interquartile range)

NA not available

incident stone diagnosis, while 27 had only returned randomly voided urine specimens. One or more stone risk factors were identified in 71 (76%) of the children tested. Seventeen (24%) had 1 risk factor only; 41 (58%) had 2 risk factors; 8 (11%)

Table 3 Analysis of urinary metabolic risk factors for kidney stones in individuals aged < 13 and ≥ 13 years

	< 13 years ($n = 61$)	≥ 13 years ($n = 129$)	p value
Patients evaluated	42 (69)	51 (40)	< 0.001
Risk factor present	32 (76)	39 (76)	0.97
Number of risk factors	2 (2–2)	2 (1–2)	0.55
24h urinary excretion			
Urine volume (mL/kg)	22.82 (14.81–33.60) $n = 27$	13.16 (8.63–16.93) $n = 39$	< 0.001
Low urine volume	14 (52)	25 (64)	0.32
Urine pH	6.0 (5.8–6.4) $n = 15$	5.9 (5.5–6.4) $n = 34$	0.53
Calcium (mmol/kg)	0.09 (0.05–0.11) $n = 26$	0.06 (0.04–0.08) $n = 38$	0.06
Magnesium (mmol/1.73 m^2)	2.44 (1.62–3.17) $n = 24$	1.45 (1.18–2.22) $n = 33$	0.01
Oxalate (mmol/1.73 m^2)	0.18 (0.14–0.21) $n = 24$	0.16 (0.10–0.21) $n = 33$	0.32
Uric acid (mmol/kg)	0.06 (0.03–0.07) $n = 25$	0.05 (0.03–0.05) $n = 37$	0.042
Citrate (mmol/1.73 m^2)	0.85 (0.16–1.44) $n = 15$	0.75 (0.36–1.01) $n = 29$	0.85
Sodium (mmol/kg)	2.31 (1.51–3.35) $n = 26$	1.77 (1.42–2.20) $n = 37$	0.12
Creatinine (mmol/kg)	0.14 (0.11–0.16) $n = 21$	0.17 (0.14–0.20) $n = 35$	0.04
Solute-to-creatinine ratio in randomly voided urine samples			
Calcium	0.60 (0.37–1.09) $n = 15$	0.45 (0.17–0.60) $n = 13$	0.06
Magnesium	0.51 (0.45–1.11) $n = 3$	0.47 (0.25–0.69) $n = 2$	0.56
Oxalate	0.04 (0.03–0.09) $n = 8$	0.02 (0.02–0.02) $n = 5$	0.11
Uric acid	0.44 (0.26–1.48) $n = 6$	0.22 $n = 1$	0.32
Citrate	0.10 (0.08–0.17) $n = 3$	0.38 (0.04–0.48) $n = 3$	0.51
Creatinine	3.73 (1.66–8.23) $n = 15$	7.50 (5.00–12.69) $n = 13$	0.02

Data are presented as number (percentage) and median (interquartile range)

had 3 risk factors; and 5 (7%) had 4 risk factors detected. Hypomagnesuria was observed in 58 children (53/57 timed and 5/5 random samples); hypocitraturia in 43 (40/44 timed and 3/6 random samples); hyperuricosuria in 22 (21/62 timed and 1/7 random samples); hypercalciuria in 19 children (14/64 timed and 5/28 random samples); and hyperoxaluria in one child (0/57 timed and 1/13 random samples). Additionally, 39 (59%) of the 66 children who had collected 24-h urine samples had low urine volume. When low urine volume was included in the risk factor assessment, 73 (78%) children had one or more risk factors identified. Although the number of risk factors identified did not differ between the sexes, girls had a significantly lower urine output standardized for body size ($p = 0.01$), and a higher number of girls met the definition of low urine volume ($p = 0.02$). The urinary excretion of magnesium, oxalate, and uric acid was also significantly lower among the girls (Table 2). Individuals diagnosed after 13 years of age had significantly lower urine volume standardized for body size compared with those diagnosed before 13 years ($p < 0.001$). The older age group also had a significantly lower magnesium and uric acid excretion (Table 3).

Stone analysis was available for only 25 (13%) patients. Of these, 15 (60%) had calcium oxalate stones, 4 (16%) had 2,8-dihydroxyadenine stones, 2 (8%) had calcium phosphate stones, 3 (12%) had struvite stones, and 1 (4%) was found to have a cystine stone.

Discussion

Our nationwide study of Icelandic children and adolescents showed an increase in the overall incidence of kidney stone disease during the years 1985–2013. This increase was mostly explained by a fourfold rise in the incidence among adolescent

girls. A modest increase in the incidence was also observed in the younger girls and in boys during the first half of the study which subsequently stabilized or trended downwards, particularly in boys who had a lower incidence at the end of the study than in the middle period.

The dramatic incidence rise observed in adolescent girls in our study resonates well with our previous finding of a similar increase in young adults, particularly young women [3]. The current findings are also similar to those of Sas and coworkers in South Carolina, who observed an increase in the incidence of symptomatic kidney stones in children and adolescents < 18 years of age [7]. In that study, the highest rise in incidence was seen in girls aged 14 to 18 years, followed by the age group 9 to 13 years. The incidence rate, however, did not change significantly in children aged < 9 years of age, which also is in concert with the findings of the present study. In another population-based study from Olmsted County, Minnesota, an increase in the incidence of symptomatic kidney stones in 12–17-year-old children was found, while no such changes were observed in those < 11 years of age [8]. The rise in incidence over time in the Olmsted County study did not differ by sex, which contrasts our findings. While no other population-based studies of the incidence of kidney stones in children are available for comparison, data derived from the Kids' Inpatient Database suggest that the prevalence of treated stone disease increased significantly between 1997 and 2003 [10]. Likewise, a recently published single-center US study found a nearly fivefold increase in the incidence of childhood kidney stone disease between the time intervals 1994–1996 and 2003–2005 [9]. It is noteworthy that the overall incidence in our study increased between 1985–1990 and 1995–2004 but, thereafter, remained relatively stable until the end of the study period, except for boys who had a significant decrease in the incidence throughout the latter half of study period. No studies on the epidemiology on kidney stone disease after the year 2007 are available for comparison.

The prevalence of kidney stones at any age is known to differ between ethnic groups and geographical areas [7, 13, 30, 31], and the reported probability of a stone event in adults is 1–5% in Asia, 5–9% in Europe, 13% in North America, and 20% in Saudi Arabia [32]. In Western nations, kidney stones are most commonly seen in non-Hispanic Caucasians, followed by Mexican Americans, while the lowest risk has been observed among African Americans [1, 30]. In North America, a considerable regional variability exists in kidney stone prevalence with the previously highest reported probability of stone disease in the Southern States (frequently referred to as the "stone belt"), which has been attributed to a warmer climate [1, 33]. However, contrasting earlier work, a recent retrospective study found stone-related hospitalizations to be more common in the North-Central region compared with the Southern States. The North-Central region is primarily inhabited by Caucasians of European descent, with similar ethnic background as our study population that lives in a country where even the summer month temperature only rarely exceeds 20 °C (68 °F). Therefore, care must be taken when interpreting these data and the potential effect of environmental heat on stone formation, as a significantly higher proportion of the Southern population is African American, the ethnic group with the lowest stone rate [13].

The female preponderance of childhood kidney stone disease observed in our study has recently been reported by other investigators [7, 10, 11]. Furthermore, our study in the adult population showed a significant increase in the incidence of symptomatic stones in the age group 18–29 years, both in men and women, and an increase of borderline significance in women aged 30–39 years [3]. Moreover, we [3] and other investigators [5, 34] have shown a decreasing male preponderance of kidney stone disease in adults, particularly in the youngest age groups, where the male-to-female ratio has become close to 1. Thus, kidney stone disease appears to be becoming more common in females, particularly among teenagers and younger adults. It will be interesting to see if a significant shift in the sex ratio in the older age groups will occur in the coming years.

The overall prevalence of stone disease in the current study remained similar in girls throughout the period studied, i.e., 1999–2013, whereas an initial increase in the prevalence among boys was followed by a decline. This likely is related to the changes observed in incidence in the same time period. However, in children the prevalence is not only linked to incidence but also depends on the number of cases turning 18 years of age each year, after which they do not contribute to the prevalence of childhood stone disease.

One or more metabolic stone risk factors were identified in approximately three quarters of the patients in our study who had undergone testing. Unfortunately, information on urinary metabolic stone risk factor evaluation was available for less than half of the study population, limiting the conclusions that can be drawn from our data. Hypercalciuria, which in earlier studies has been reported to be present in 75–80% of pediatric stone formers [14, 15], was found in only 20% of the children tested in the present study. Hypomagnesuria and hypocitraturia, which were the most commonly noted stone risk factors in our study sample, have only rarely been found to be highly prevalent among children with kidney stone disease [35]. As our University Hospital's Clinical Biochemistry Laboratory has been running a quality control program for decades, we do not think our results are affected by incorrect urinary solute or creatinine measurements. The low 24-h urine volume we observed in teenagers is similar to that recently reported by others [36]. Nevertheless, teenage girls in our study had a significantly lower urine volume and 24-h urinary magnesium excretion compared with boys, while other studies have not shown differences in

urinary stone risk factor profiles between the sexes [36, 37]. As both of these risk factors do promote lithogenicity, they may have contributed to the high incidence in our teenage female population.

The lifestyle and dietary habits of the Icelandic population, including children and adolescents, appear to be similar to those observed among other affluent industrialized nations [38]. To that end, the mean BMI as well as the prevalence of obesity and type 2 diabetes have markedly increased among Icelanders over the past 30–40 years [39]. While no scientific data associate stone formation with food intake in the Icelandic childhood population, the sodium consumption observed in a dietary survey carried out in Icelandic children and adolescents in the years 2002–2003, exceeded the recommended daily intake in the majority of participants, regardless of sex [39]. Generous sodium consumption is known to increase stone risk [40, 41], which in our study was rather moderate and does not explain the sex difference we observed.

It is not clear what causes the dramatic increase in the incidence of kidney stone disease in teenage females while no changes were observed in younger girls or boys of any age. One can only speculate that the combination of the current Western diet and the teenage female hormonal milieu, including oral contraceptive use, may adversely affect the urinary factors governing lithogenicity. In addition, differences between the sexes in hydration and the type of beverage consumed may also play a role and warrant further study.

The use of CT scanning for the diagnosis of stone disease increased markedly during the study period; this predominantly occurred after the year 2004 when the stone incidence did not change significantly. Therefore, the more frequent use of highly sensitive imaging techniques such as CT does not appear to explain the rise in incidence nor does it explain the sex difference in kidney stone incidence observed.

Although the majority of the individuals in our study were healthy aside from the stone disease, the substantial number of children with monogenic stone disease and other underlying medical conditions or congenital anomalies of the kidneys and the urinary tract underscores the importance of a thorough medical evaluation of all children with nephrolithiasis [20].

The strengths of the current study include a population-based research design where practically all Icelandic children and adolescents who developed their first kidney stone during the period of the study were identified and included. The Icelandic population is primarily White with a genetic background reflecting the gene pool of Northern Europeans [42], and the lifestyle and dietary habits are comparable to other affluent industrialized nations. Thus, we believe our data are representative for Western populations. A limitation of the study is, however, the retrospective design. Further, even though our study included a relatively large number of patients for a pediatric study and probably captured more than 95% of Icelandic children with symptomatic kidney stones, the study population is rather small and our search strategy may have missed individuals with mild or short-lived symptoms. Moreover, incomplete data hamper our ability to draw firm conclusions regarding metabolic stone risk factors and the potential association of body composition with stone risk.

In conclusion, the current study showed a fourfold rise in the incidence of symptomatic kidney stone disease in adolescent girls in the last three decades. On the other hand, the incidence in boys decreased significantly in the latter part of the study period. Limited or no changes in the sex ratio were observed in prepubertal children. The overall female predominance of stone disease in adolescents and young adults in the Icelandic population may reflect a change in the sex ratio of stone formers. The increase in incidence observed in teenage females is poorly understood and warrants further study since it may herald changes in the sex ratio of kidney stone disease in adults.

Acknowledgements Preliminary results of this study appeared in an abstract form at the Biennial Meeting of The Icelandic Society of Internal Medicine in Reykjavik in October 2010, and the Annual Meeting of The American Society of Nephrology in Denver, CO, USA, in November 2010. The authors want to thank Loftur Ingi Bjarnason, Computer Scientist at Landspitali–The National University Hospital of Iceland, for data management and programming.

Funding The study was supported by the Landspitali University Hospital Research Fund. The study sponsor had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. Drs. Edvardsson and Palsson are supported by the Rare Kidney Stone Consortium (U54KD083908), a part of the National Center for Advancing Translational Sciences' (NCATS) Rare Diseases Clinical Research Network (RDCRN), which is an initiative of the Office of Rare Diseases Research (ORDR). The Rare Kidney Stone Consortium is funded through collaboration between NCATS and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Compliance with ethical standards

The study was approved by the Icelandic National Bioethics Committee (NBC 03-002-S1-AG1) and the Icelandic Data Protection Authority. The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC (2003) Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 63:1817–1823

2. Romero V, Akpinar H, Assimos DG (2010) Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol 12:e86–e96
3. Edvardsson VO, Indridason OS, Haraldsson G, Kjartansson O, Palsson R (2013) Temporal trends in the incidence of kidney stone disease. Kidney Int 83:146–152
4. Trinchieri A, Coppi F, Montanari E, Del Nero A, Zanetti G, Pisani E (2000) Increase in the prevalence of symptomatic upper urinary tract stones during the last ten years. Eur Urol 37:23–25
5. Du J, Johnston R, Rice M (2009) Temporal trends of acute nephrolithiasis in Auckland, New Zealand. N Z Med J 122:13–20
6. Yasui T, Iguchi M, Suzuki S, Kohri K (2008) Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. Urology 71:209–213
7. Sas DJ, Hulsey TC, Shatat IF, Orak JK (2010) Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr 157:132–137
8. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD (2012) Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol 188:247–252
9. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, Trachtman H (2007) Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol 177:2300–2305
10. Matlaga BR, Schaeffer AJ, Novak TE, Trock BJ (2010) Epidemiologic insights into pediatric kidney stone disease. Urol Res 38(6):453–457
11. Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR (2009) Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. Urology 74:104–107
12. Pietrow PK, Pope JCI, Adams MC, Shyr Y, Brock JWI (2002) Clinical outcome of pediatric stone disease. J Urol 167:670–673
13. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, Tong L, Baker LA (2010) Hospitalizations for pediatric stone disease in United States, 2002-2007. J Urol 183:1151–1156
14. Bergsland KJ, Coe FL, White MD, Erhard MJ, DeFoor WR, Mahan JD, Schwaderer AL, Asplin JR (2012) Urine risk factors in children with calcium kidney stones and their siblings. Kidney Int 81:1140–1148
15. Edvardsson V, Elidottir H, Indridason OS, Palsson R (2005) High incidence of kidney stones in Icelandic children. Pediatr Nephrol 20:940–944
16. Coe FL, Parks JH, Asplin JR (1992) The pathogenesis and treatment of kidney stones. N Engl J Med 327:1141–1152
17. Milliner DS, Murphy ME (1993) Urolithiasis in pediatric patients. Mayo Clin Proc 68:241–248
18. Coward RJM, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, van't Hoff WG (2003) Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child 88:962–965
19. Bevill M, Kattula A, Cooper CS, Storm DW (2016) The modern metabolic stone evaluation in children. Urology 101:15–20
20. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, Palsson R (2013) Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol 28:1923–1942
21. Cochat P, Pichault V, Bacchetta J, Dubourg L, Sabot JF, Saban C, Daudon M, Liutkus A (2010) Nephrolithiasis related to inborn metabolic diseases. Pediatr Nephrol 25:415–424
22. Edvardsson V (2016) Urolithiasis in children. In: Avner ED et al (eds) Pediatric Nephrology. Springer, Berlin, pp 1821–1868
23. Penido MG, Srivastava T, Alon US (2013) Pediatric primary urolithiasis: 12-year experience at a Midwestern Children's Hospital. J Urol 189:1493–1497
24. Battino BS, De FW, Coe F, Tackett L, Erhard M, Wacksman J, Sheldon CA, Minevich E (2002) Metabolic evaluation of children with urolithiasis: are adult references for supersaturation appropriate? J Urol 168:2568–2571
25. Lande MB, Varade W, Erkan E, Niederbracht Y, Schwartz GJ (2005) Role of urinary supersaturation in the evaluation of children with urolithiasis. Pediatr Nephrol 20:491–494
26. Pak CY, Poindexter JR, Adams-Huet B, Pearle MS (2003) Predictive value of kidney stone composition in the detection of metabolic abnormalities. Am J Med 115:26–32
27. Levy FL, Adams-Huet B, Pak CY (1995) Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med 98:50–59
28. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL (2000) CDC Growth Charts: United States. Adv Data 314:1-27
29. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL (2002) Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 109:45–60
30. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project (2012) Prevalence of kidney stones in the United States. Eur Urol 62:160–165
31. Routh JC, Graham DA, Nelson CP (2010) Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol 184:1100–1104
32. Ramello A, Vitale C, Marangella M (2000) Epidemiology of nephrolithiasis. J Nephrol 13(Suppl 3):S45–S50
33. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H (1994) Demographic and geographic variability of kidney stones in the United States. Kidney Int 46:893–899
34. Lieske JC, Pena de la Vega LS, Slezak JM, Bergstralh EJ, Leibson CL, Ho KL, Gettman MT (2006) Renal stone epidemiology in Rochester, Minnesota: an update. Kidney Int 69:760–764
35. Tefekli A, Esen T, Ziylan O, Erol B, Armagan A, Ander H, Akinci M (2003) Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: is there any difference? Urol Int 70:273–277
36. Peres LA, Langer SS, Schmidt RC, Nacke RA, Francescon PV, Almeida RC, Coimbra RM, Ribas TM, Barros TD, Matsuo T (2011) Nephrolithiasis in pediatric patients: metabolic and anatomical investigation. J Bras Nefrol 33:50–54
37. Elmaci AM, Ece A, Akin F (2014) Clinical characteristics and metabolic abnormalities in preschool-age children with urolithiasis in southeast Anatolia. J Pediatr Urol 10:495–499
38. Steingrimsdottir LT, Thorgeirsdottir H, Olafsdottir AS (2003) (The Icelandic National Nutrition Survey 2002). https://www.landlaeknir.is/servlet/file/store93/item11603/skyrsla.pdf
39. Gunnarsdottir I, Helgadottir H, Thorisdottir B, Thorsdottir I (2013) (Diet of six-year-old Icelandic children—national dietary survey 2011-2012). Laeknabladid 99:17–23
40. Taylor EN, Fung TT, Curhan GC (2009) DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol 20:2253–2259
41. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A (2002) Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 346:77–84
42. Helgason A, Nicholson G, Stefansson K, Donnelly P (2003) A reassessment of genetic diversity in Icelanders: strong evidence from multiple loci for relative homogeneity caused by genetic drift. Ann Hum Genet 67:281–297