ORIGINAL REPORT

Biochemical Risk Factors for Stone Formation in Healthy School Children

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Received: 4 Apr. 2012 ; Received in revised form: 26 Aug. 2012; Accepted: 28 Aug. 2012

Abstract- Prevalence of urolithiasis in childhood is increasing. The wide geographic variation in the incidence of lithiasis in childhood is related to climatic, dietary, and socioeconomic factors. Many children with stone disease have a metabolic abnormality. In Southeast Asia, urinary calculi are endemic and are related to dietary factors. The main aim of this study was to determine the prevalence of renal stone, urine metabolic abnormality, control of blood pressure and demographic character in elementary school children of Qom. A cross sectional study was performed on 110 primary school children (56 girls and 54 boys) aged 7 to 11 years old. Demographic data such as age, height, weight were gathered, and systolic and diastolic blood pressure, Urine analysis and culture, urinary levels of calcium, creatinine, phosphorus, magnesium, sodium, potassium, uric acid, cystine, citrate, oxalate, protein and sonographic findings were evaluated. The mean (±SD) of age was 8.85±1.51 years. Only one child had renal stone (1%), but the prevalence of abnormal renal sonography was 7%. The most prevalent urine metabolic abnormalities were hypercalciuria (23%) and hypocitraturia (100%). 11.2% of children had positive urine culture that all were female. The prevalence of high blood pressure was 7.1% for girls and 11.1% for boys. The prevalence of renal stone in children in this study was 1%, which means the accurate judgment about the prevalence of renal stone in Qom city needs more comprehensive studies. Similar to other studies in Iran this study shows that the prevalence of hypercalciuria is significantly higher comparing to other countries, it may be associated with excessive intake of sodium.

Acta Medica Iranica, 2012; 50(12): 814-818.

Keywords: Children; Hypercalciuria; Hypocitraturia; Urolithiasis

Introduction

Urolithiasis has becomes more common in children over the past few decade. In recent years, the prevalence of urinary stones in children is increased. The suspected etiologies are lifestyle, diet and lack of adequate amounts of fluids and drugs uses (1-3). Kidney stones in Turkey, Pakistan and some parts of South Asia, Africa and South America are endemic (4-7).

Prevalence of urolithiasis in Turkey is 0.08% (2). Enough information about the prevalence of this problem does not exist in Iran. Worldwide prevalence of the disease is 1-15% (8-11). Iran is in the "belt stone" and the prevalence of urinary stone in Iran is 2-3% (4-7). Almost all the patients have urinary metabolism disorders (12-14).

The incidence of kidney stones in children is less than adults. Urinary tract calculi account for between 1 in 1000 and 1 in 7600 hospital admissions in children and adolescents in the United States, a rate that is approximately 1/50th–1/75th that reported in adults (13).

An explanation for the lower incidence and prevalence of urolithiasis observed in children than in adults is incomplete, but may be related to urinary citrate and magnesium in children are more than adults, as well as substances that prevent adhesion of urinary crystals to renal epithelial cells are more in the children (8,10).

Studies have shown that the rate of urinary stones is increased five times in the past decade, in part because, there is more accurate diagnostic methods (3). Kidney stones in men is four times more common, although in

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children varies. The boys have 1.4-2.1 times more risk than girls for the stone formation (13,15-17).

Rapid diagnosis, treatment and prevention are essential to prevent renal failure. Urolithiasis in children and adolescents, like that in adults, frequently recurs. Recurrence rates are higher in children with demonstrable metabolic abnormalities. The authors have reported recurrence rates of 20-40% with variable follow-up periods (13). Based on prevalence of kidney stones in neighboring countries and also the lack of similar studies in Iran, the clinical manifestation, etiology and prevalence of urinary stones were studied in primary school children in the city of Qom between 2009-2010 (5). This study was done to obtain information on urinary metabolism disorders, urinary infections incidence , high blood pressure and urinary stone risk factors such as renal anatomic diseases.

The definition of children's height and weight in relation to age and sex and urine, were other objectives of this study.

Materials and Methods

Cross-sectional study at Children's Hospital, Nephrology Division, Qom University of Medical Sciences and Health Services on 110 healthy primary school children (56 girls and 54 boys) between 2008 and 2009 was performed. Children age was 7 to 11 years. Parental agreement was documented and then were questioned about the history of urinary tract infections, blood pressure and familial history for the stone. Children were examined by a General Practitioner and demographic information such as age and height were recorded. Blood pressure (BP) was also measured after 5 minutes rest in sitting position.

According to the International Protocol (1996) systolic or diastolic BP that equal to or more than 95 percentile for age, sex and height were considered abnormal. The genitourinary tract sonography was performed with Medison SA8000 sonographic machine (free of charge). Parents were trained to collect morning urine samples.

Data were analyzed using Excel and SPSS. The minimum and maximum, mean and standard deviation variables were determined. Using regression analysis, t-test and ANOVA the data were studied in relation to risk factors. $P<0.05$ was considered as statistically significant difference.

Results

This cross-sectional study was performed in October 2008 to June 2009 to determine the biochemical risk factors and prevalence of kidney stones in healthy children in primary schools in the city of Qom.

In this study, 110 apparently healthy children from elementary schools in Qom were enrolled using a cluster sampling method. Fifty-six children (51%) were females and 54 children (49%) were male. The age range was 7-12 years old. The average age was 9.2±1.4 years for girls and 8.5±1.5 years for the boys. Girls' average weight was 33.8±11.1 kg. Body weight ranges from 16.6 to 58.6 kg. The boys average weight was 30.3±7.9 kg and body weight 17 kg to 66 kg. A significant difference between the mean weight of children, boys and girls ($P=0.082$) was not observed.

Average height of the girls was 135.75±11.55 cm (range: 115-162 cm). The average male height was 129.88±10.69 (range 106-156 cm). There was no significant difference between girls and boys in their height ($P=0.07$).

Children's average systolic BP was 105.6±11.7 mm Hg (range: 80-135 mmHg). Average systolic BP in females was 102.8±13.3 mmHg (range: 80-135 mmHg). Average systolic BP in males was 108.4±0.95 (range: 90-130 mmHg). A significant differences between girls and boys in mean systolic BP ($P=0.011$) was observed.

Overall, the average diastolic BP of children studied was 67.3 ± 4.7 mm Hg (range: 50-80 mmHg). The average diastolic BP of the girls was 66.6±5.1 mmHg (range: 50-70 mmHg). The average diastolic BP of boys was 68±4.3 mmHg (range: 60-80 mmHg). We did not observe a significant difference in mean diastolic BP between girls and boys ($P=0.133$).

Ten children had hypertension (9.1%), 4 female (7.1%) and 6 males (11.1%). There was no significant relationship between high BP and sex ($P=0.523$, Odds ratio: 1.625, CI: 0.432-6 0.111). In the 9 patients (8.2%), systolic BP was increased and in one the patient both systolic and diastolic BP was abnormal.

In two patients (20%) with high BP, weight percentile was greater than or equal to 95% and in 8 (0.80%) between 5-95% percentile. In children with normal BP, 10 patients (10%) weight percentile was greater than or equal to 95%, 82 (82%) had percentile of weight between 5-95 percent and 8 patients (8%) had a weight less than or equal to 5% percentile. The data showed no significant correlation between BP and children's weight percentile ($P=0.441$).

Among children with high BP, one (10%) had height percentile greater than or equal to 95% and 9 patients (90%) had a height of between 5-95 percentile. In children with normal BP, 7 patients (7%) with percentile of height greater or equal to 95%, 87 patients (87%)

percentile of height between 5-95% and 6 patients (6%) had a height less than or equal to 5% percentile. The data showed no significant difference between BP and height of children (*P*=0.697).

In the analysis of urine samples, mean urine pH was 5.4±0.61. In patients with normal BP, mean pH was 5.4±0.63 and in patients with high BP, urine pH was 5.3±0.42. Thus, no significant difference in urine pH was detected (*P*=0.475).

The median urine specific gravity (SG) was 1021.69. In 31 of 110 patients (28.4%) SG was 1025, the average SG in normal patients with normal BP was 1021.4±27.7 and in patients with high BP was 1024.7±29.2. Therefore no significant difference in urine SG could be (*P*=0.172).

One patient (0.9%) had red blood cell in the urine samples, 6 patients had white blood cells (5.5%), 6 patients had nitrite in urine samples, 2 patients (1.8%) glucose, 5 patients (5.4%) protein, and 9 patients (8.3%) had bacteria in their urine sample.

21 patients (9.1%), had crystal in the urine, the three cases (7.2%) were triple phosphate, 5 cases (5.4%) calcium oxalate and 13 patients (11.8%) amorphous crystals, also 7 cases (4.6%) had epithelial cells in their urine.

In this study, 18 patients (7.2%) had abnormal calcium/creatinine ratio, 12 patients (11.4%) oxalate to creatinine, 8 patients (8.9%) of uric acid to creatinine, 1 (0.9%) protein to creatinine, 5 cystine to creatinine and 104 patients had abnormal urinary citrate to creatinine ratio.

A total of 107 urine cultures were performed. In 95 cases (88.8%) urine cultures were negative. And in 5 cases (4.5%) Gram-positive was cultured. Culture was positive for *E. coli* in one person (0.9%), and in 5 patients (5.4%) contamination was observed.

All patients who had positive cultures (11.2%) were female. Our data showed a significant association between positive urine culture and gender (*P*<0.001, CI=0.544-0.343).

In 3 patients who had negative cultures (2.3%) and in 3 patients who had positive cultures (2.5%) white blood cells (WBC) were seen in their urine samples.

The data showed no significant relation between positive urine culture and WBC in urine samples (*P*=0.18, CI=1.58-793.279) .

106 of 110 patients (96.4%) had normal ultrasound but one (0.9%) had hydronephrosis, 1 patients had kidney stones and 2 patients (1.8%) had double ureter.

27 patients (25.2%) had increased wall bladder thickness, that 24 of these 27 cases (3.25%) had negative cultures, means no statistically significant difference exist between the results of urine cultures and bladder wall thickness (*P*=0.1, CI=2.05-9.34).

Discussion

According to the previous reports, estimation of the exact prevalence of urinary stones in children is difficult. The Middle East and countries like Iran and Turkey are endemic for urinary stones (2,15). Pinduli *et al*. studied the incidence of urinary stones in 1086 normal people (20). Stone prevalence was 3.96%. The prevalence in men (4/35), was slightly more than women (3/62). In their study, urinary tract stone was not seen in people under 20 years. Over the past decade, the most important cause of kidney stones in children diverted from infection to abnormal metabolic factors. Kidney stones secondary to infection in Great Britain decreased from 63% to 30% in the past 30 years (16).

Van Der Woortk *et al*. study was carried out in two periods (1994-1996 and 2003-2005), in the first period, 7 of all the studied patients had stone while in the second period the number of patients was 61 (3). This means that the prevalence of urinary stones was increased 4.6 times (3).

In this study, the most common (52%) metabolic disorder was hypocitraturia, followed by hypercalcurea. Also risk of urinary stone recurrence was about 40% (3). Sönmez *et al*. studied 2252 children, mean age was 8.57 years (from 15 days to 15 years). Urinary calcium/creatinine was 0.092. Hypercalciuria was seen in 9.6% (normal upper limit=0.21). Urine calcium/creatinine ratio did not have statistical relation with either sex, diet regiment, weight, length, family history or drinking water calcium levels (21).

Berçem *et al*. studied 592 healthy children (308 boys and 284 girls, age 3 months to 16 years) in Turkey and evaluated hypercalciuria and calcium to creatinine ratio in the second urine sample morning .Hypercalciuria in 17 children (9/2%) were found (9 boys and 8 girls), with positive family history of kidney stones in 50% of children who had asymptomatic hypercalciuria. The ratio calcium/creatinine had no statistical relation with sex and age (22).

Negri *et al.* studied 799 people with kidney stone (462 males and 337 females)(23). Their results showed that in women the body mass index (BMI) increased significantly with increased urinary excretion of uric acid, oxalate, phosphate, creatinine and sodium. But no change in the renal excretion of calcium, magnesium, citrate and urine pH was observed (23). Increased BMI

levels in men occurred with increased excretion of oxalate, uric acid, creatinine and phosphorus, sodium, magnesium and citrate, no change occurred in urinary calcium levels, but urine pH was significantly reduced (23).

In a study by Dursun *et al*. in Turkey between 1998 and 2005, 179 children with kidney stones were studied. The average age was 4.5 years in time of the kidney stones diagnosis. The most important initial clinical symptoms was abdominal or flank pain (55.9%)(11). Urinary tract infection was present in 20% of patients during hospitalization. 0.24% of patients had anatomic abnormalities (11). The most common anomaly was ureteropelvic junction obstruction. Family history of kidney stones in children was seen in 54.7% of patients. Hypercalciuria in 42.3% and 54.8% of patients found to have hyperuricosuria and the most common type of stone was calcium oxalate (11).

Bak *et al*. also studied 72 children who had urinary stone (2-168 months) in Turkey (24). Metabolic urinary stone was seen in 33% by which 30% were due to anatomic urinary problems. Infections caused in 26% and 11% were idiopathic (24). 18% of patients had a positive family history for kidney stones. All patients had upper urinary tract stones in the kidney. 24% of patients had multiple stones in both kidneys. The most common type of stones were calcium oxalate. Among patients with metabolic stones, hypercalciuria and hyperoxaluria were observed in 21% and hypocitraturia was seen in 85% of patients (24). Studies in Turkey also showed that the most common causes of kidney stones are due to abnormal urinary metabolism. Studies in Europe, showed that 44% of kidney stones are created by anatomical abnormalities, infection in 30%, 14% idiopathic and 12% are associated with metabolic disorders (16,17).

Dalirian *et al*. approached 109 patients suffering from kidney stones (51 males and 58 females). Analysis showed that in 50% of them, calcium oxalate stones were formed (25). Also hypercalciuria in 25% and hyperuricosuria in 19% were found (25).

In our study, 100% patients had hypocitraturia. Hypercalciuria was observed in 23%. 11.4% had hyperuricosuria, 8.4% hyperoxaluria, 8.9% cystinuria and finally 1.2% had proteinuria.

Idiopathic hypercalciuria can be due to increased intestinal calcium absorption or impaired renal reabsorption. In many studies hypercalciuria is the most common metabolic disorder for stone formation (16,18,19).

In our study 23% of children had hypercalciuria, while a similar study in Turkey, 2.9 percent of healthy children had hypercalciuria (21). Low citrate excretion in our patients may have an important role in the pathogenesis of kidney stones (4). Hypocitraturia is related to distal tubular acidosis, chronic diarrhea, hypokalemia or urinary tract infection, but usually it is unclear why, as in our study, so is named as idiopathic.

Incidences of hypocitraturia in our study shows need further investigation in this geographic area (4) urinary tract infections produce urease formation that increases susceptibility to the stone formation (1). In the present study 11.2% of patients had positive cultures, all of which were female and infection was created by *E. coli* or Gram-positive cocci. We believe that the regional climate, nutritional status, metabolic disorders, urinary tract infections and the high incidence of kidney stones in Qom children is a major issue which needs to be addressed in future.

Because kidney stones can cause severe kidney damage and kidney failure, so fast diagnosis and appropriate treatment also prevention recurrence program is very important. Thus, in all children with kidney stones, urinary metabolic evaluation and sonographic anatomic evaluation should be done especially in those who have a positive family history of kidney stones. All children should be encouraged to eat adequate fluids throughout the day.

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