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Prevalence and Pathophysiology of Pediatric Urolithiasis - A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Urolithiasis is a condition in which hard deposits made of salts and minerals are accumulated inside the kidneys. A lot of studies demonstrated adult urolithiasis but studies on pediatric urolithiasis is still scarce. Studies had shown that pediatric urolithiasis prevalence is progressively increasing

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worldwide. The main cause for this increase is not totally clear but has been associated to changes in climate, nutritional habits and other environmental factors. Pediatric urolithiasis is distinctive and different from adult urolithiasis concerning prevalence, etiology and clinical presentation. Over the time while the condition was evolving, the main cause has changed from predominantly infectious to metabolic in nature. Pediatric urolithiasis should not be underestimated as it is associated with morbidity mainly since it possesses a striking feature which is ability to recur. Metabolic risk factors are more communal in pediatric urolithiasis than in adults. The common type of calculi in children is comprised of either calcium oxalate or calcium phosphate mainly and is often associated with a metabolic abnormality. Informed as metabolic abnormalities, Idiopathic hypercalciuria and hypocitraturia are the most frequently reported. A good understanding of the causes and risk factors of pediatric urolithiasis will provide better strategies and techniques for calculi treatment and prevention in children.

Keywords: Pediatric; urolithiasis; epidemiology; prevalence; pathophysiology.

1. INTRODUCTION

Urolithiasis is a condition in which hard deposits made of salts and minerals are accumulated inside the kidneys. Urolithiasis is a worldwide problem; it is a well-known common disease in adults with a predicted prevalence of 3% to 5% [1]. Urolithiasis has been increasing and growing in children in the past decades, as was shown by recent studies, not only in near east and Far East countries but also in economically developed and industrialized countries [2]. Still, some studies demonstrate that prevalence of pediatric stone formation in western countries is lower than its prevalence in Asia and Middle Eastern countries, also studies showed different calculi composition and location between those regions [3-5]. As perceived that the endemic calculi observed in developing countries are often limited to the bladder and comprise mostly ammonium acid, urate, and uric acid, and seem to relate with a decreased availability of dietary phosphates [6]. In addition, in the United States, calculi are found in the kidneys or ureters, comprise either calcium oxalate or calcium phosphate, and often associated with a metabolic abnormality [7].

Pediatric urolithiasis is distinctive and different from adult urolithiasis concerning prevalence, etiology and clinical presentation. The expected prevalence in the United States from 1950s to 1970s is nearly 1% to 2% that of adults [8]. Pediatric urolithiasis should not be undervalued as it is associated with high rates of morbidity mainly since it possesses a striking feature which is recurrence. There is no technique of stone removal reduces or changes the recurrence morbidity in pediatric patients which is directly associated with surgical interventions and morphological changes resulting from potential obstructions of the urinary tract along with their clinical manifestations [9]. The prevalence and clinical manifestations of urinary stones in pediatrics vary in relation to geography and historical periods. This variation is related to climate, genetic and dietary factors and socio-economic factors [10-12]. Understanding the risk factors of renal calculi can help in categorizing risks in an individual patient and can lead to conducting specific measures to prevent calculi recurrence. Some of the risk factors for pediatric urolithiasis include: individual's susceptibility to form stones, such as genetic predisposition and gender and metabolic abnormalities, and environmental factors that enable stone disease, such as dietary lifestyle besides local climate characteristics [13]. Kidney stones are endemic in some regions as Southeast Asia, the Middle East, India, and Pakistan; on the contrary, calculi are scarce in children of African descent. Also in the United States, calculi seem to be more communal in Caucasian children from the Southeastern area. Moreover, in the last 3 decades the cause of pediatric urolithiasis in the United Kingdom has changed from predominantly infectious to metabolic in nature [14]. Calcium oxalate and calcium phosphate stones are the most common types of calculi; they are detected in more than 75% of all children assessed when compared with adults [7,15]. In addition, infectious stones are the second most common type of calculi which represent 15–25% of all children assessed [7,16,17].

2. EPIDEMIOLOGY

The prevalence of urolithiasis in adults varies from prevalence of pediatric urolithiasis. The possibility that an individual develop renal stones differs according to the geographical distribution. The incidence of urolithiasis raised from 1-5% in

Asia, to 5-9% in Europe, 12% in Canada and 13-15% in the USA, though Asian countries at high risk as Saudi Arabia has high incidence of 20.1% [18,19]. Pediatric urolithiasis exemplifies 2-3% of the total number of patients of calculi [20]. Of the factors affecting the occurrence of urolithiasis are geographic area, racial distribution, dietary habits, socio-economic status of the population, and local conditions and practices may also have impact. As we mentioned before, variations in socio-economic status and the consequent variations in dietary habits have affected not only the prevalence, but also the location and chemical composition of the stone. In economically developed countries, reno-ureteral urolithiasis calculi comprising chiefly calcium oxalate and phosphate are found to be more common, while in Asia, vesical urolithiasis are more common with calculi comprising mainly ammonium urate and calcium oxalate [21]. Worldwide epidemiology studies stated that about 60% to 90% of stones found in children are formed of calcium oxalate, seconded by 10% to 20% formed of calcium phosphate, 1% to 14% of struvite, 5% to 10% of uric acid, 1% to 5% of cysteine, and 4% mixed or miscellaneous [22-32].

A study demonstrated that the incidence of urolithiasis in population in Europe in the 19th century was similar to the incidence of urolithiasis in population in Asia in the 20th century [33].

The prevalence of urolithiasis in the United States is expected to be responsible for 1 in 7,600 to 1 in 1,000 admissions of pediatric hospital. In asymptomatic children in Turkish primary school the incidence of pediatric urolithiasis is said to be 1% [34]. In Venezuela through 1998, prevalence of urolithiasis of general outpatient consultations in all children's' hospitals was 7% [35]. In Ethiopia, a hospital-based study from reported that 13% of entry admissions were because of urolithiaisis, and almost 50% of these entry admissions aged 0-19 years [36] The incidence may even be higher than what is reported by the hospital-based studies, as patients with asymptomatic calculi might be dismissed. This problem was reflected by a cross-sectional study conducted in Scotland on 3398 randomly-chosen patients, as the prevalence was 3.5% of X-ray-recognized calculi in the upper urinary tract [37].

The reason of regional and geographic variability in urolithiasis prevalence is multi-factorial. According to studies in the United States, the risk of developing kidney stones increases from the West to the East and from the North to the South [38]. The high prevalence of urolithiasis in the United States had caused this area to be labeled as the "stone belt" or also called "kidney stone belt"; this term refers back to 1976, and it is applied to the areas in the Southeast USA that comprises Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia and Kentucky as shown in Fig. 1 [13].

There is also the Afro-Asian kidney stone belt, which extends from Sudan, Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia to Philippines. Within the same kidney stone belt, the prevalence of urolithiasis differs greatly due to different local conditions and practices. Another study conducted in Italy shows also regional and geographical variations, as it demonstrates higher risk of stone prevalence in South of Italy compared to the North of Italy.

3. PATHOPHYSIOLOGY

As we mentioned before, studies showed that urolithiasis is associated with a recognizable metabolic abnormality in about 40% to 50% of children [7,14,15,39]. The chief metabolic abnormalities are: hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, and hyperuricosuria. Hypercalciuria or hypocitraturia are the most commonly reported pediatric abnormalities [40]. For example in the United States about 40% to 65% of stones found comprise calcium oxalate, 14% to 30% comprised of calcium phosphate, 10% to 20% comprised of struvite, 5% to 10% comprised of cysteine, and finally 1% to 4% comprised of uric acid [7,41].

Formation of crystals in urine is a complex and multifaceted process which is mostly stimulated or inhibited by some physicochemical or anatomic factors. Of the main factors responsible for this process, the total urine volume, the excretion of some of the risk factors, urinary supersaturation of certain ions, urinary pH, tubular flow rate and developmental anomalies of the urinary tract are the commonly seen factors. All types of stones are uncommonly formed in dilute urine. Certain organic or inorganic ions inhibit crystallization of calcium oxalate and calcium phosphate, which are citrate, magnesium, pyrophosphate, certain

glycosaminoglycans, nephrocalcin, and phytates. Citrate inhibits the formation of calcium stones and binds to urinary calcium, thus forming a soluble complex in urine, then available free ionic calcium essential for calcium oxalate or calcium phosphate supersaturation are reduced; in addition citrate also inhibits calcium crystals aggregation and growth [42,43]. On the other hand, uric acid stimulates calcium oxalate supersaturation, in which the crystal base of the material allows the growth of the second mineral that it is in the same supersaturating orientation.

Another crucial factor affecting calculi formation is the PH of the urine as it affects the saturation of some potential stone forming ions by shifting their solubility and increasing their tendency to aggregate, whereas acidic urine reduce the solubility and thereby increases aggregation of some crystals as pH less than 6 lowers the solubility of uric acid and pH less than 7.5 lowers solubility of cysteine. On the other hand, alkaline pH more than 6 is usually the stimulating factor for the precipitating of struvite and calcium phosphate stones, while calcium oxalate precipitation is not affected by changes in pH of urine as long as it is within the physiological range. When the surface of focal point (nidus) permits nucleation, growth, and aggregation of stone particles at low concentrations, the crystals in the urine starts to form. Infection, foreign body, and Randall plaques are considered as uroepithelial damage and act as nidus. In the basement membrane in the loop of Henle originates the crystals of calcium phosphate which made up the Randall plaques. The expected reason for most cases of idiopathic calcium oxalate stones is the nidus which is formed of the aggregation of crystals and then merged into plaques in the interstitium and finally ejected through the uroepithelium of the renal papillae. Calcium oxalate calculi comprise two forms which are monohydrate (whewellite) or dihydrate (weddellite). Either form of these calcium oxalate calculi is mixed with small amounts of calcium phosphate, thereby forming the starting nidus of the stone [44].

4. SIGNS AND SYMPTOMS

Symptoms and clinical presentation seen in adults and adolescents vary differently from the symptoms seen in children. As in adults, the normal findings of renal colic are seen like abdominal or flank pain varying in severity and maybe radiating to the groin. The typical or classical symptom and complaint in children is nonspecific and non-localized pain either in the abdomen, flank, or pelvis [45].

In 10% to 14% only of all pediatric cases endure the typical renal colic symptoms, while the majority endure non-localized abdomen pain, gross or microscopic hematuria, and urinary tract infection (UTI) [46]. Also some general clinical presentations may be present such as nausea, vomiting, anorexia and malaise. 30% to 55% of all pediatric urolithiasis patients comprise gross or microscopic hematuria [14,46]. Some studies demonstrated that approximately 10% of pediatric urolithiasis patients have symptoms of lower urinary tract disorder as nocturnal and/or diurnal enuresis, urgency and/or urinary incontinence, suprapubic or urethral pain [47,48,49]. Also some studies demonstrate that 15% to 25% of pediatric urolithiasis patients are asymptomatic and need more care and attention [14,40].

5. MANAGEMENT

Accessing the epidemiology and pathophysiology of pediatric urolithiasis aims mainly to set up proper management, prevention, and treatment strategies. Management has two main lines to follow, either management of acute pediatric urolithiasis or non-acute pediatric urolithiasis. First the diagnosis should be confirmed using suitable imaging and laboratory tests.

The goals of management should be settled first to ensure the most benefits. Goals of management of pediatric urolithiasis are ensuring complete clearance of stones, treating complications, correcting metabolic or anatomic abnormalities, preventing stone recurrence, preventing UTIs, and preserving of renal functions [50].

The first line of management is controlling pain caused by the movement of the stone, and this is achieved by using narcotic analgesics as morphine, non-steroidal anti-inflammatory drugs (NSAIDs) as ketorolac, or/and antispasmodics as n-scopolamine butylbromide [6,51]. NSAIDs may be considered as drugs of first choice as they possess benefits more than just reducing pain. Of these benefits, preventing or relieving ureteral oedema, peristalsis and pelvic pressure caused as a result of the attempts to eliminate the stone, as NSAIDs mechanism of action include inhibition of prostaglandin synthesis [52]. The most important management measure that should be done is drinking water and keeping the

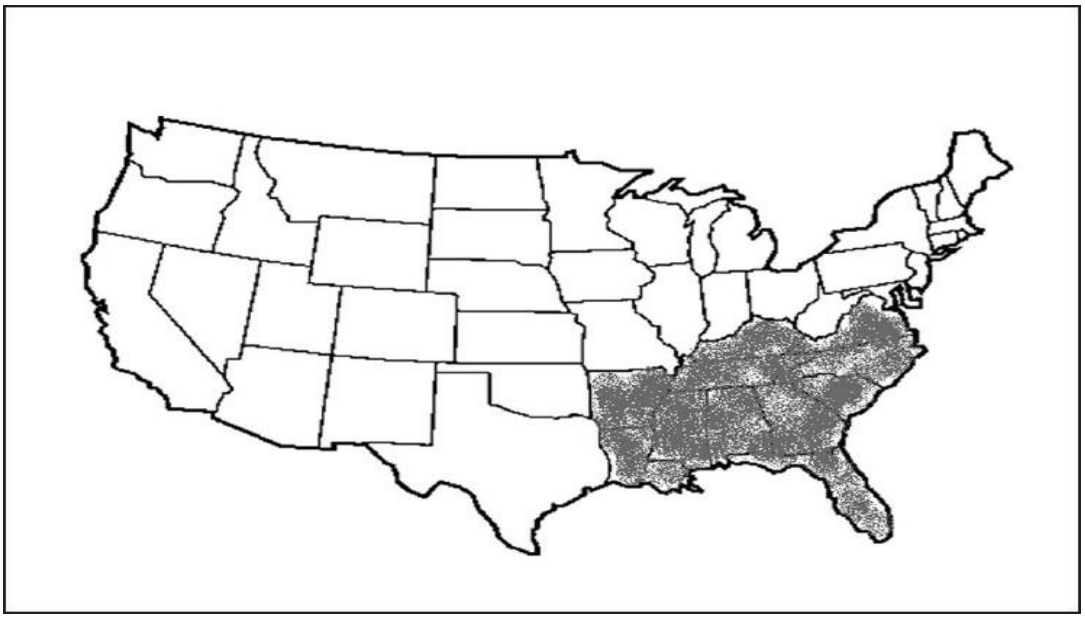

Fig. 1. Stone belt in North America [13]

patient hydrated, as hydration increases urine flow, thus reducing the supersaturation level of salts as calcium, oxalate, phosphate, uric acid, and cysteine which are responsible for stone formation [53]. Urine flow should be equal to or even higher than 1 mL/kg to be effective as protection against kidney stone formation; water or fluid intake should be distributed over the 24 hours of the day, but should not pass two liters [54]. In case of patients who are unable to drink parenteral hydration is the adequate management measure for this case. If the patient had whole obstruction, intravenous infusion rate of 1.5 to 2 times preservation is required. Some pharmacological agents that may promote the passage of stones and reduce symptoms could be used, as alpha-adrenergic blocker like tamsulosin and calcium-channel blocker like nifedipine; they had shown encouraging results in adult patients with distal calculi in the ureter [55].

6. CONCLUSION

The prevalence of pediatric urolithiasis has increased worldwide over the last few decades. Adult urolithiasis differs from pediatric urolithiasis in many aspects including the symptoms, pathophysiology, epidemiology, and composition of the stone. Existing epidemiological data demonstrate high diversity of pathophysiological data for recurrent stone disease. The form of stone disease has altered, with an increase in kidney stones comprising calcium oxalate or calcium phosphate and a decrease in bladder stones composed of ammonium and urate. Acknowledgement and awareness of geographical variations is necessary to make an appropriate examination and evaluation of the patient with urolithiasis, and also to know the risk factors of each region so patients can avoid them, and therefore setting a proper treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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