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RESEARCH ARTICLE

UROLITHIASIS IN CHILDREN.

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Abstract

Background: Urolithiasis is a worldwide problem can affect the children but in lower incidence than in adult. In KSA the incidence of urolithiasis become higher than in the past and twice common than in west countries. Urolithiasis is different in incidence, prevalence and characters of stones according to many factors like history of the patient, diet and geographical location.
Objective: The objective of this article is to review the incidence and prevalence of urolithiasis in different countries, risk factors of urolithiasis formation, how can diagnose and treat urolithiasis.
Method: This review article was based on 25 articles, various in their types. This article collected from different resources; PubMed, BMJ, Oxford, Ovid, Springer and up to date databases. Including and excluding criteria was use in it.
Conclusion: Each single year the incidence of urolithiasis is raising for several causes one of them is genetic predisposition which strongly depend on consanguineous marriages. There are other risk factors such as diet, ethnicity and anatomical abnormalities. For diagnosis, there are several techniques but the most common and beneficial one is CT without contrast. Invasive and non-invasive interventions are the types of urolithiasis treatment depend on the best intervention for the patient according to the doctor estimation.

Introduction:-

Stones are aggregates made up of crystals and protein present within the kidney or urinary tract.[1] stones are developed by subsequent growth and aggregation of crystallized ions.[2] There are many factors influencing urolithiasis formation; which are urine volume and flow, concentration of the ions and urinary PH.[2]

Urolithiasis in children is a worldwide problem, it is uncommon and only 1-3% of kidney stones occurs in children, but the incidence is believed to be on rise. The recent report from UK suggests that males are more likely to suffering from urolithiasis in their first decade of life, but in second decade in females. [2]

The prevalence, incidence, composition and characteristic of urolithiasis in children vary due to geographical location and historical periods differences. This variation is also related to climate, genetic, dietary factors and socio-economic factors. [3]

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Urolithiasis in children are most common in non-Hispanic Caucasians, then Mexican Americans, and the lowest risk in African Americans. [7]

In UK there is a clear increase in the prevalence of urolithiasis in children over the past 30 years. The incidence ratio in boys and girls is 2.1:1, where the median age is 36 months for males and 48 months for females.
The causes of urolithiasis in children in UK are variable, but the most common cause is metabolic abnormality (44%), then infection (30%), while in 26% of cases no etiological factor could be detected. [4]

In Iceland, the incidence of urolithiasis in children is higher than other western countries. The incidence is higher in female than males. The median age at diagnosis was 9.4 years (range 0.2-14.9). [5]
The family history was positive in one third of patient. The other causes of urolithiasis in Icelandic children is metabolic abnormality in 96% of cases, where hypercalciuria the most common metabolic risk factor (78%). [5]

In Turkey, Pediatric urolithiasis is an endemic disease. The incidence is higher in males (69.4%) than females (30.6%), The ages ranging from 2 to 168 months. [7]

Metabolic and anatomic causes of urolithiasis are commonly found in young age compared to other causes of urolithiasis. [6] The clinical risk factors of urolithiasis in children are (idiopathic) hypercalciuria, hyperoxaluria, hypocitraturia, low urine volume and hyperuricosuria. These risk factors have been reported in 40-95% of pediatric stones former. [7]

The main risk factor of kidney stones in children is a metabolic abnormality. 76% of children with urolithiasis have metabolic abnormality. Metabolic evaluation and regular checkup are very important for children who suffered from urolithiasis before because they have a high incidence of recurrent stones formation. Additionally, recurrent obstruction may place their growing kidneys at risk. [8]

There is also a genetic aspect of pediatric urolithiasis, so the individual with urolithiasis are more likely to have a family history of kidney stones disease.

Twins studies also showed that, the probed concordance rate in monozygotic twins (32.4%) was significantly greater than in dizygotic twins (17.3%). [1]

The clinical presentation and features of children with urolithiasis is varied but nonspecific abdominal pain and irritability are the most common feature. Also, microhematuria is seen in most affected children rather than gross hematuria which is the presenting sign in 30–50 % of cases only. Other features like urinary tract infection, lower urinary tract symptoms such as dysuria, frequency and voiding problems can be seen. [7]

For diagnosis of children suspected with urolithiasis, there are several preliminary things to do it; like medical history, physical examination, laboratory evaluation and Imaging which contribute significantly towards management. [7]

Management of children with acute symptomatic stones, the most effective thing is intravenous ketorolac then intravenous opioids, these relieve pain due to urinary obstruction. Some analgesic can be added if needed. For stones larger than 5–10mm in diameter immediate surgical intervention is the main cornerstone. There are a range of surgical techniques available. In children where stone size ranges from 4-5mm, spontaneous expulsion can be augmented with medical therapy provided there is no history of pain and infection. At least a period of two weeks should be given after the medical therapy, and if it fails surgical intervention can be considered. [7]
I choose this topic for my review article because urolithiasis in children is rare and has lower incidence than adolescents but is worldwide disease.

This review article intends to look into the causes, prevalence and incidence, diagnosis and treatment of kidney stones in children which is a rare problem but has a significant impact on health of an individual.

Materials and Method:-

This research is a review article about urolithiasis in children. The research strategy that was followed in this review article was based on collection of articles that talked about urolithiasis in children, its prevalence, risk factors, diagnosis, management and treatment. About 25 articles were included in the review article. Most of types of

medical research were included in the review such as systematic reviews, meta-analysis and cohort studies. Most of the articles were collected from the published articles in PubMed, BMJ, Oxford, Ovid, Springer and up to date databases. The review was done by using some key words and medical phrases such as kidney stones, kidney stones in children, urolithiasis and nephrolithiasis. The information and data were collected by reading the articles and extract the needed information from it. Most of the articles that talked about urolithiasis specially in children were included in the review. There was categorization used in the review, so the review talked only about the children, but all nationalities and ethnics were included. Articles that was going deeply in the treatment of the disease, articles that talked about specific risk factor and articles which talked about urolithiasis in adult were excluded from the review. The review defined urolithiasis specially in children, its risk factors, diagnosis and treatment. Also, the review illustrates urolithiasis disease prevalence among different children from different countries.

Discussion:-

1. Stones begin to form in collecting system (kidneys, urinary bladder) or in tubules. [9]
2. Stones are formed from soluble salts. Calcium Oxalate is the most common type of stone, which is a soluble salt which can exist in dissolved, solid or crystalline form. [10]
3. When the soluble salt concentration in the solution is high enough, then the precipitation process will begin to form solid crystals from the soluble salt. [10]
4. There are many of chemical element in the urine which can participate to form soluble salt. these chemical elements in normal condition found in a dissolved form in the urine. The concentration of these chemical elements or salts are high in the urine, because the presence of inhibitors in the urine which make the formation of soluble salt crystals difficult. [10]
5. Some of these urolithiasis inhibitors are substance of our diet, while the other inhibitors are formed by our bodies proteins which help in prevent stones formation. [10]
6. Nucleation is the process of stones formation, start when the factors which inhibiting salt crystal to develop less than factors encouraging salt crystals formation. Over the time, these crystals become bigger and result in a detectable kidney stone if the conditions in urine remain favorable for stone formation. [10]
7. Incidence and prevalence:
8. The kingdom of Saudi Arabia is a large country, and also has a high child population percentage. About 29.4% of the population is children which aged ranged between 0-14 years. The growth rate of the child population is 1.54%. [11]
9. In Saudi Arabia the expectancy of stone formation is high especially in male in different ages. The formation of idiopathic calcium stones in Saudi Arabia is higher and common than in children in the West. Lifestyle factors and dietary habits make these differences between different populations. This what ElFaqih and Hussain wrote in epidemiological chapter of management in lithiasis book. [12]
10. In UK there has been a shift in incidence and prevalence of urolithiasis in children over the past 30 years. There are variable risk factors of it, most of them are known as metabolic abnormalities, this what Coward et al mentioned in their article. [4] (Fig 1)

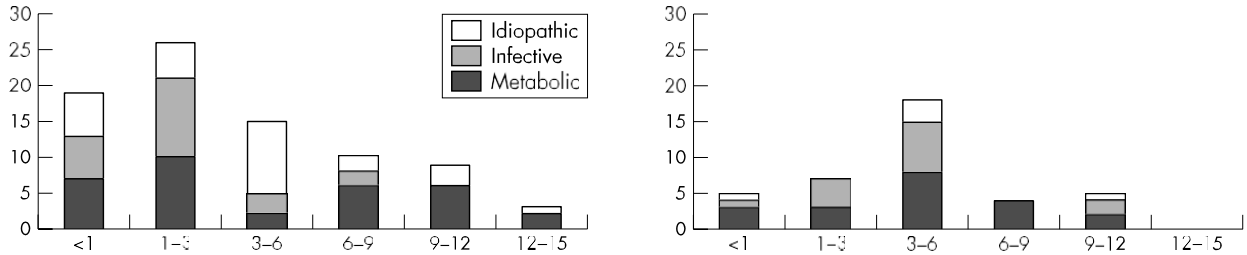

Figure1:-Age at presentation, sex distribution, causes of renal stones diseases in UK children (A) Males (B) Females

This figure has been reproduced as it is from Coward R. Epidemiology of pediatric renal stone disease in the UK. Archives of Disease in Childhood. 2003;88(11):962-965

Edvardsson et al [5] mentioned that in Iceland, urolithiasis is a common disorder with 10% to 15% of estimated lifetime risk. About 50%–75% of recurrence rate within 10 years of diagnosis. About 75-80% of children with urolithiasis have hypercalciuria, which is the most common metabolic risk factor for stones formation.

Also, Edvardsson et al [5] mentioned that, in the other western countries the kidney stone is a common disorder with an estimated lifetime risk of approximately 10-15% and the rate of kidney stone recurrence within 10 years of diagnosis is 50-75%. In north America, about 7% of children less than 16 years diagnosed with Nephrolithiasis. The male to female ratio which diagnosed with Nephrolithiasis 1–1.5:1. In in the United Kingdom, the incidence of kidney stone in children is two children per million, and kidney stones account for 0.13 to 0.94/1000 of pediatric hospital admissions in the United States.

Causes:

Sarica [13] mentioned some of risk factors that cause urolithiasis in children, one of this is Hypercalciuria (excessive urinary calcium excretion), is the most common cause of kidney stones in children. About 34% of all cases of pediatric kidney stones is caused by Hypercalciuria. The normal calcium excretion is 4 mg/kg during childhood which is measured in a 24 hours urine collection with the patient consuming a routine diet, preferably confirmed with second sample values greater than 0.2 in a 24-h urine sample are considered elevated. About 46% of pediatric patients with Hypercalciuria have a positive family history of urolithiasis, which confirmed that, the Hypercalciuria is a heredity and also is one of genetic causes of kidney stone. The genetic basis of Hypercalciuria is unknown but it seems to follow an autosomal dominant pattern of inheritance and can be diagnosed in approximately 4% of an unselected pediatric population.

The other cause is Hyperuricosuria (excess of uric acid or urates in the urine), the uric acid is formed as the end product of purine metabolism. About 8% of children with stones have Hyperuricosuria. Hyperuricosuria also lead to calcium oxalate lithiasis. There are two factors which contribute in promotion of uric acid precipitation: high urine saturation of uric acid and pH of urine <5.8. Hyperuricosuria can present in overproduction of uric acid or normal level of uric acid. [13]

Spivacow et al [1] put Hypercalciuria, Hyperuricosuria and other causes such as Hypomagnesuria, Hyperoxaluria, Cystinuria and Hypocitraturia under metabolic abnormalities which cause urolithiasis in children. (Table 1)

Table 1:-metabolic risk factors for pediatric urolithiasis and their Incidence. [1]

Metabolic risk factor	N (%)
Hypocitraturia	17 (18.8)
Hypercalciuria	17 (18.8)
Hypomagnesuria	6 (6.7)
Hyperuricosuria	3 (3.3)
Hyperoxaluria	3 (3.3)
Cystinuria	1 (1.1)
Total	47 (52.2)

Adapted from Spivacow F, Negri A, del Valle E, Calviño I, Fradinger E, Zanchetta J. Metabolic risk factors in children with kidney stone disease. PediatrNephrol. 2008;23(7):1129-1133.

90 of urolithiasis patients who their ages under 16 years between 2–16 years, the mean age was 10.7 years and the male to female ratio was 1.14:1.0 (48 males and 42 females) to continue their routine diet. Two 24 hours urine samples obtained, followed by 2 hours fasting urine samples collected by spontaneous voiding on the morning of the following day. During this period of urine collection, the urine was kept refrigerated. Urine samples were analyzed for creatinine, calcium, uric acid, magnesium, oxalate and citrate. Blood samples drawn is the next step of urine collection, blood samples were analyzed for calcium, creatinine, uric acid and magnesium. The volume of urine for both 24 hours groups was measured. Ph and urinary sediment were determining in 2 hours fasting sample. there are criteria for diagnosis metabolic risk factor of urolithiasis: hypercalciuria, >4 mg/kg per day; hyperoxaluria,>50 mg/1.73 m2 BSA (body surface area) per day; hypocitraturia, <400 mg/g creatinine; hypomagnesuria,< 1.24 mg/kg per day; hyperuricosuria,>815 mg/1.73 m2 BSA per day. At the end of study, the evaluation of metabolic risk factors showed that 84.4% of all cases had one or more metabolic abnormality, while there were no metabolic abnormalities in 15.6%. [1]

Another common cause of metabolic abnormality is Hypocitraturia (low citrate level in the urine), that result from metabolic acidosis or hypokalemia. [8]

In Spivacow et al [1] article, Hypocitraturia mentioned as the second most common metabolic abnormality, it is found in 37.8% of children with urolithiasis. recently, Hypocitraturia was considered to be very infrequent. In Tefekli, Turkey 60.6% of children with urolithiasis have Hypocitraturia.

Hypocitraturia in Turkish series is in high frequency, it is related to local dietary habits or other regional causes. Recently, in New York series, also Hypocitruria was the most common metabolic abnormality. Between 2003-2005 there is a study on children with urolithiasis, about 52% of them have Hypocitaruria. Hypocitraturia was more prevalent among pediatric patients than adult patients (37.8% vs. 23%), while the frequency of Hypocitraturia was similar. [1]

Hyperoxaluria is another metabolic cause of urolithiasis in children was mentioned in pediatric stone chapter in clinical management of urolithiasis book, which wrote it by Sarica and Horuz [14]. Oxalate is an end product of normal purine and amino acid; liver is the site of this process. There are two types of hyperoxaluria; primary and it is a rare autosomal recessive disorder caused by hepatic alanine glyoxylate transferase deficiency or glyoxylate reductase/ hydroxyl pyruvate reductase. Secondary type may occur due to ingestion of large amount of vitamin C, sarcoidosis, malabsorption states, ethylene glycol poisoning, RTA, pyridoxine deficiency. About 20% of children with nephrolithiasis have Hyperoxaluria.

Also, Cystinuria mentioned as one of metabolic causes of pediatric urolithiasis. [14] Cystinuria is an autosomal recessive disorder. Cystinuria is abnormal in reabsorption of cysteine and the dibasic amino acid in renal tubular and intestinal absorptive transport. About 6-8% of children with urinary calculi have Cystinuria. Cystine crystals form in children with high excretion, Which the normal is 1,000 m mol/L (240 mg/L) in normal urine.

Nelson et al [15] in the article added the anatomical abnormalities as a cause of urolithiasis, such as ureteropelvic junction (UPJ) obstruction or ureterovesical junction (UVJ) obstruction, which found in 11-24% of children with urolithiasis.

Ureteropelvic junction (UPJ) obstruction is a congenital condition, which there is a blockage or narrowing at the point between the ureter and part of the kidney called renal pelvis. This condition can be detected by ultrasound before birth. [16]
Ureterovesical junction (UVJ) obstruction, refer to blockage at the area of meeting between ureter and urinary bladder. This obstruction cause impaired in urine flow and this lead urine to back up into and dilate the ureter and kidneys (megaureter and hydronephrosis).[17]

Clinical presentation:
Penido and Tavares mentioned in their article[3], The pediatric patient with urolithiasis is show with pain in the abdomen, which is the main compliant. In 10-14% of all pediatric cases are present with gross or microscopic hematuria and uncharacteristic abdominal pain. The other general manifestations associated with abdominal pain such us vomiting, nausea, malaise and anorexia may be present. About 10% of pediatric patient with urolithiasis have signs and symptoms of lower urinary tract dysfunction (urethral pain, urinary incontinence, suprapubic pain). About 15-25% of pediatric patients with urolithiasis, specially the younger ones are need more attention because they are asymptomatic.

Diagnosis:
Taking family history is very important in urolithiasis diagnosis and is the first step in begin of the diagnosis, which Baştuğ and Düşünsel mentioned [21]. The aim of history taking is to determine whether other family member have urolithiasis, gout or renal disease. The history should include questions of prematurity, malabsorption which caused by gastrointestinal disease, enteral or parenteral nutrition rich in calcium, oxalate, protein, sodium and phosphorus. All these factors will influence the treatment options of urolithiasis.

Physical examination is the second step, in infants and younger children might have agitation or discomfort; in other instances, patients can be asymptomatic. [21]

Also, urinalysis and microscopic evaluation should do it in urolithiasis diagnosis, for pyuria, crystals, hematuria and the presence of bacteria. Measurement of blood and urine PH is important in diagnosis of distal renal tubular acidosis. For exclude the possibility of a chronic or acute UTI, should perform urine culture [21].

For urolithiasis, there are several ways for diagnosis which Fordham et al [18] mentioned in their article, the first one is CT without contrast, is the best and the gold standard for urinary tract imaging in the presence of stones. CT gives an accurate measurement, localization, morphology, characterization of stones density and body habitus all of this can predict if the fragments of stone response to the treatment. For high specificity and sensitivity using a combination of US an CT in selected cases.

Ultrasound is also another one of the diagnostic technique for urolithiasis as Strohmaier mentioned[20]. Easily available, avoiding radiation and non-invasive are some of ultrasound advantages, but it is dependent on the skills of the doctor in performing.

b-mode ultrasonography can detect the stones in the proximal and distal ureter and in the kidney. The stones in other regions of the ureter cannot visualized due to intestinal gases. About 61%-93% is the percentage of the sensitivity and specificity of ultrasound in diagnosis of urolithiasis. The detection rate of stones was higher in the kidney when compared to the ureter. [20]

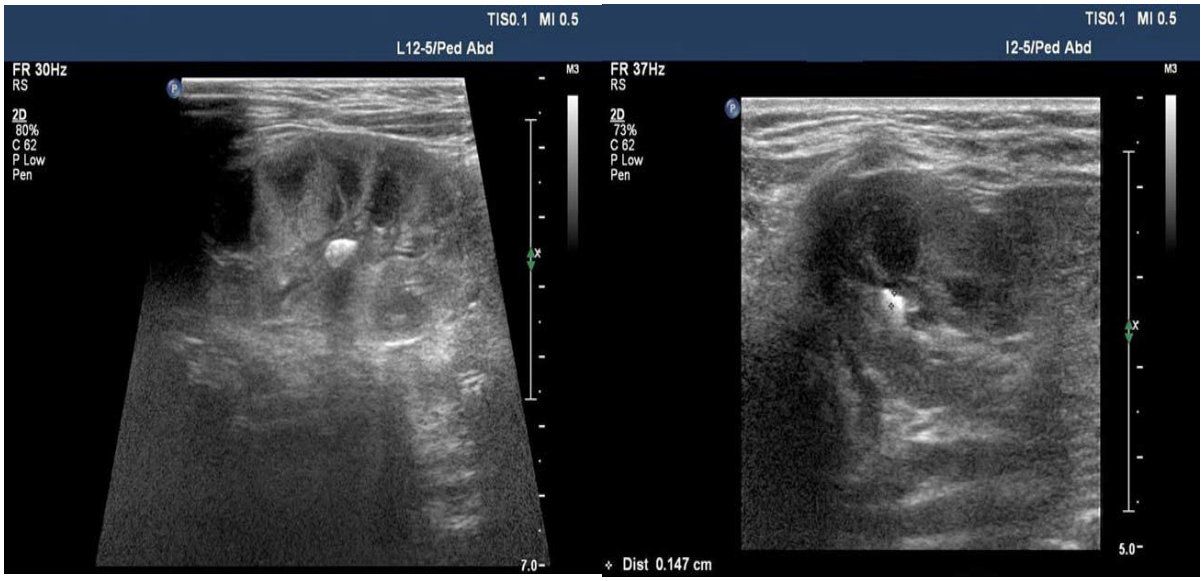

Fig 2a:-Image of the kidney(ultrasonography): male,10 months old, left kidney profile. The 0.6×0.4-cm2 calculus at the renal calyx has a light shadow[19]

Fig 2b:-Image of the kidney(ultrasonography): female,8 months old, right kidney profile. A 0.15-cm2 sand-like calculus (marked with +) at the renal calyx with a comet-like tail [19]

This figure has been reproduced as it is from Sun Q, Shen Y, Sun N, Zhang G, Chen Z, Fan J et al. Diagnosis, treatment and follow-up of 25 patients with melamine-induced kidney stones complicated by acute obstructive renal failure in Beijing Children's Hospital. European Journal of Pediatrics. 2009;169(4):483-489.

Drug name	Dosage	Formulation	Indication
Allopurinol	10 mg/kg per day. Single or divided 2–3doses	Tablet: 100mg, 300 mg. Oral solution: can be made from tablets	Hyperuricosuria
Captopril	0.5–1.5 mg/kg per dose. Given 2–4 times per day (lower starting dose in	Tablet: 12.5 mg, 25 mg, 50 mg. Oral solution: 1 mg/ml may be prepared	Cystinuria

	infants)		
Chlorothiazide	10–20 mg/kg per day divided 1–2 doses	Tablet: 250mg, 500 mg. Oral solution: 250 mg/5 ml	Hypercalciuria, Hyperoxaluria
Hydrochlorothiazide (HCTZ)	1–2 mg/kg per day divided 1–2 doses	Tablet: 25 mg, 50 mg. Oral solution: 50 mg/5 ml	Hypercalciuria, Hyperoxaluria
Moduretic	Based on HCTZ	Tablet: (HCTZ50mg/am	Hypercalciuria, Hyperoxaluria
Potassium (K) citrate	0.5–1.5 mEq K/kg per day. Divided 2 doses (tablets) or 3 doses (liquid) (titrate higher if needed)	Tablet: 5 mEq K, 10 mEq K. Solution: 2 mEq K/ml	Hypocitraturia, Hypercalciuria, Hyperuricosuria, Cystinuria
Pyridoxine (vitamin B6)	25-200 mg/day, once daily (titrated to effect with urine oxalate levels)	Tablet: 25 mg, 50mg	Primary Hyperoxaluria
Tiopronin	15 mg/kg per day divided 3doses	Tablet:100mg	Cystinuria
D-Penicillamine	30 mg/kg per day divided 4 doses, half at night	Capsule:125mg, 250mg	Cystinuria

Table 2:-Medication commonly used in the treatment of urolithiasis.

Fordham et al [18] mentioned Plain films (KUB) type of abdominal radiograph, are useful for detection, measurement, localization of radiopaque calculi. It is the best for performing in calcium-containing stones greater than 3mm located over the kidneys or bladder. Scout KUB exams are less sensitive and specific for stone detection than conventional KUB.

Treatment:

First line of urolithiasis treatment is changing the diet and lifestyle, was mentioned by Jackson and Reeber [22]. Children are recommended to stay well hydrated to produce 35ml of urine per Kg daily. More urine output equal more decrease in the saturation of calcium oxalate, uric acid, calcium phosphate. Stop drinking of soda-pop or sweetened juice with high fructose corn syrup, because these increase the risk of kidney stones formation.

Sodium consumption should be limited to less than 2-3mEq/kg/day for young children. There is a relation between sodium consumption and increasing calcinuria. The amount of sodium in urine reflects the sodium in the diet. Also, the calcium consumption should be limited, because it is directly associated with urolithiasis. [22]

For pharmacological treatment of urolithiasis, there are a wide range of medication were mentioned by Uri S. Alon [23] for each cause of urolithiasis. (table 2)

Adapted from Alon U. Medical treatment of pediatric urolithiasis. PediatrNephrol. 2008;24(11):2129-2135.

There are several types of procedures to treat urolithiasis in children, the standard procedures do not differ from those used in adult. The main four types, which were mentioned by Michael et al [24] are ESWL, ureterorenoscopy (URS), percutaneous nephrolithotomy (PCNL), and-in selected cases-laparoscopic surgery.

Extracorporeal shock-wave lithotripsy (ESWL) is used for urolithiasis treatment, it is safe and effective as mentioned by Michael et al [24]. It has many types, the main function of all its types is to generate and focus the shock-wave energy at stones, then the stones become small fragments and can pass the ureter.

Ureterorenoscopy (URS)is a good applicable tool and routinely available. There are two types rigid and flexible endoscopes. URS is ideally for used in calculi, which located in mid and distal ureter.

There is study mentioned by Michael et al [24] in the article, which comparing between two groups; one of them treated by URS and the other group treated by (ESWL). The result showed 94% of patients were free of stones by (URS) treatment, but on the other hand 43% treated by (ESWL).

EI-Damanhoury et al [25] mentioned percutaneous nephrolithotripsy (PCNL) as surgical treatment, which is the most common procedure for perfusion and drainage of an obstructed area; dilation of uretropelvic junction. One of the advantages of the percutaneous nephrolithotripsy is that the pediatric stone disease often infectious or metabolic in origin, and the other types of surgical procedures were required for recurrent stone disease. It is used for stones removing from upper part of ureter. percutaneous nephrolithotripsy have a contra-indication with blood coagulation disorder. The successful rate of this procedure does not affect by Composition and the size of the stone.

Michael et al [24] said that 0.3-5.4% of children with urolithiasis are treated by open surgery / laparoscopic surgery, especially in patients with anatomical abnormalities- i.e. ureteropelvic junction obstruction, obstructive megaureter, urolithiasis.

Conclusion:-

Urolithiasis is a worldwide problem but is less common in children than adult. There are many aspects in children are similar in adult, but clinical presentation, diagnosis and interventions are different and unique in children. The prevalence and incidence of urolithiasis in children appears to be increase for several causes; one of them is a genetic cause, which lead to metabolic or anatomical abnormalities, so consanguineous marriages should be limited. These genetic predispositions are trigger by unhealthy diet and lifestyle. Flanking pain and hematuria are most common symptoms presenting in child with urolithiasis. For diagnosis, fistful start with taking a full history, then examination, after that urinalysis, at the end using imaging techniques. There are invasive and non-invasive treatment for urolithiasis depend on what is the best for the patient.

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