INTRODUCTION

Urolithiasis is a universal problem, affecting patients across geographical, cultural, and racial boundaries ***(Moe et al., 2002).***

The prevalence of urinary stones has progressively increased in the industrialized nations, and a similar trend is being observed in developing countries due to changing social and economic conditions ***(Curhan, 2007).***

Approximately 1.2 million Americans are affected annually, and it is estimated that up to 14% of men and 6% of women will develop stone disease during their lifetime ***(Stamatelou et al., 2003).***

In addition, many patients will be affected by multiple stones throughout their lifetime, with estimated recurrence rates of 50% within 5–10 years and 75% within 20 years ***(Scales et al., 2007).***

Thus, it is not surprising that different clinical guidelines on urolithiasis, which appeared in recent years, do not hesitate to point out the analysis of the calculus as an essential element and starting point in studying the disease. ***(Straub et al., 2005).***

The exclusive removal of the calculus, without conducting an adequate study of the causes that led to its formation, is only the suppression of the expression of a disease that will repeatedly cause new episodes. Often, some bad eating habits explain why a calculus developed. However, at other times, the calculus is due to metabolic disorders, of genetic origin or acquired, whose early diagnosis is of great importance not only to prevent relapses, but also to establish the most appropriate therapeutic measures to prevent or delay the appearance of associated renal, osseous or cardiovascular complications ***(Domingos and Serra, 2011).***

Also, knowing the composition of a urinary calculus is frequently a key factor in determining its most appropriate management. Should the urine be alkalinized? Will the stone be amenable to extracorporeal shock wave lithotripsy, or should ureteroscopy or percutaneous lithotripsy be attempted? ***(Tiselius et al., 2006).***

Although clinical guidelines include the need to analyze the calculi, they say little or nothing about what the methodology to be used is, and when they declare themselves on this aspect, infrared spectrometry (IRS) and X-ray diffraction are the most mentioned techniques ***(Thomas, 2009)***.

Chemical methods have repeatedly proved to be unreliable in numerous quality control programs, with error rates in identifying certain components above 90%, so they should be definitely abandoned ***(Hesse et al., 2005).***

The IRS is based on the interaction of infrared light with the covalent bonds of the compounds present in the calculus, leading to the emergence of some characteristic bands that make their identification possible. Its main advantages are that it can be applied on very small samples (less than 1 mg) and that it allows for the identification of both crystalline and amorphous substances (proteins, amorphous phosphates, lipids, etc.). But the need for experience in the identification of the spectra and the lack of other applications in routine laboratories mean that the IRS is available at very few centers. The IRS has a high analytical quality and practicability, and it is considered as a very useful methodology in the study of the calculus ***(Singh, 2008).***

AIM OF THE WORK

1- To detect stone composition in a group of stone formers in the Egyptian community by Infra-red spectroscopy.

2- To relate the physical and chemical features of the stones to their density on plain x-ray of the urinary tract (PUT/KUB) and non-contrast spiral CT (NCSCT).

Chapter (1)

URINARY LITHIASIS: ETIOLOGY, EPIDEMIOLOGY, AND PATHOGENESIS

Although stone disease is one of the most common afflictions of modern society, it has been described since antiquity. Revolutionary advances in the minimally invasive and noninvasive management of stone disease over the past 2 decades have greatly facilitated the ease with which stones are removed. However, surgical treatments, although they remove the offending stone, do little to alter the course of the disease ***(Pearle et al., 2005).***

Epidemiology of renal calculi:

The lifetime prevalence of kidney stone disease is estimated at 1% to 15%, with the probability of having a stone varying according to age, gender, race, and geographic location. In the United States, the prevalence of stone disease has been estimated at 10% to 15% ***(Stamatelou et al., 2003).***

In Japan, the incidence of nephrolithiasis has doubled over a 40-year time period, both in men and women. These increases were most prominent in the last 10 to 20 years, with

rates among men increasing sharply since the 1990s, and rates among women increasing more gradually since the 1980s ***(Yasui et al., 2008).***

Gender:

Stone disease typically affects adult men more commonly than adult women. By a variety of indicators including inpatient admissions, outpatient office visits, and emergency department visits, men are affected two to three times more often than women ***(Pearle et al., 2005).***

This finding and the lower incidence of stone disease in women compared with men have been attributed to the protective effect of estrogen against stone formation in premenopausal women, owing to enhanced renal calcium absorption and reduced bone resorption ***(Heller et al., 2002).***

Race/Ethnicity:

Mente and colleagues (2007) attempted to identify genetic influences on stone disease by comparing stone prevalence among different ethnic groups residing in the same geographic region. Using Europeans (Caucasians) as the reference group, the relative risk of calcium stones was higher in individuals of Arabic; West Indian; West Asian; and Latin American origin in descent ***(Mente et al., 2007).***

Age:

Stone occurrence is relatively uncommon before age 20 but peaks in incidence in the fourth to sixth decades of life ***(Hiatt et al., 1982).***

Geography:

The geographic distribution of stone disease tends to roughly follow environmental risk factors; a higher prevalence of stone disease is found in hot, arid, or dry climates such as the mountains, desert, or tropical areas ***(Robertson, 2003).***

Climate:

Chen and colleagues analyzed monthly inpatient and outpatient medical benefit claims for a primary diagnosis of renal or ureteral calculi or renal colic and found that the peak incidence of stone-related claims occurred in July through September, with a sharp decline in claims in October ***(Chen et al., 2008).***

Body Mass Index and Weight:

Recent evidence linking obesity and insulin resistance with low urine pH and uric acid stones ***(Maalouf et al., 2004)***, as well as an association between hyperinsulinemia and

hypercalciuria could account for an increased risk of uric acid and/or calcium stones in obese patients ***(Nowicki et al., 1998)***.

Subjects with higher BMI excreted more urinary oxalate, uric acid, sodium, and phosphorus than those with lower BMI. Furthermore, similar to other studies, urinary supersaturation of uric acid increased with BMI. It has been suggested that the association of obesity with calcium oxalate stone formation is primarily due to increased excretion of promoters of stone formation ***(Negri et al., 2007).***

In contrast, the association of obesity and uric acid stone formation is primarily influenced by urinary pH ***(Daudon M et al., 2006).***

Water:

The beneficial effect of a high fluid intake on stone prevention has long been recognized. In two large observational studies, fluid intake was found to be inversely related to the risk of incident kidney stone formation ***(Curhan et al., 1997).***

Physicochemistry:

State of Saturation:

In order for a urinary calculus to form, the urine must contain an excess of the crystalline material that can generate a stone. That is to say, the urinary environment must be

supersaturated with these stone-forming crystals. To better elucidate this concept, it is instructive to consider urinary saturation (figure 1) ***(Coe FL et al., 2005).***

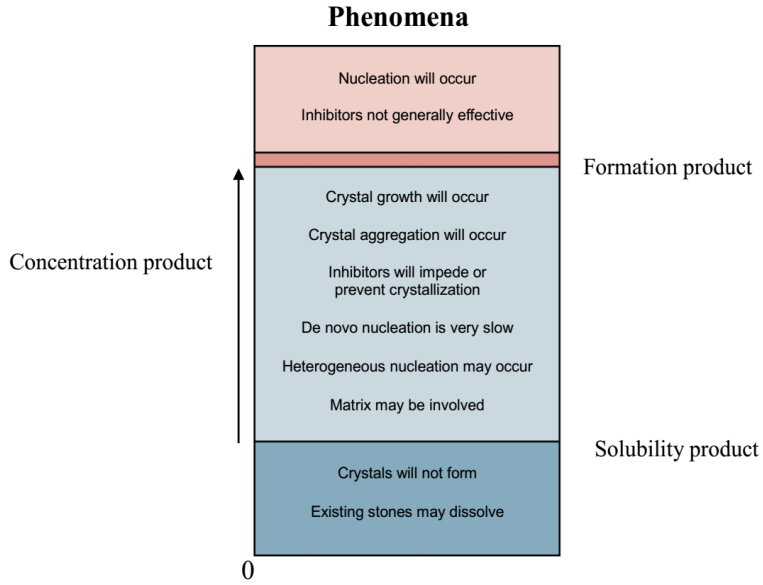

Figure 1: States of saturation. Listed are solid-solution phenomena that are likely to occur at a given range of concentration products. Three general situations are considered: (1) concentrations less than the solubility Product (undersaturation), (2) concentrations that are metastable with respect to de novo Precipitation (between the solubility product and the formation product), and (3) concentrations that are greater than the formation product (unstable) ***(From Michael et al., 2012).***

For all solutions, urine included, there is a maximum amount of dissolved salt that can be kept in a stable solution. The concentration at which urine becomes saturated with the dissolved salt and crystallization begins is known as the thermodynamic solubility product (*Ksp*). *Ksp* is a mathematical expression, equal to the product of the concentration of the pure

chemical components of the solute at the point of saturation. For example, the *Ksp* for sodium chloride is [Na+] [Cl-]. When the concentration of the salt in a solution is less than the solubility product, the solution is said to be undersaturated. No spontaneous crystallization will occur in an undersaturated solution; therefore, in undersaturated urine, stones will not form. As the concentration of the salt increases above its solubility product, there will be a second point encountered where the solution becomes unstable with respect to the salt and crystallization will spontaneously begin; this point is termed the formation product. The region between the solubility product and the formation product is known as the metastable region. When a solution is metastable with respect to a salt, de novo crystallization is unlikely to occur, although growth may occur on existing crystals ***(Asplin JR et al., 1997).***

Nucleation

Nucleation is the establishment of the smallest unit lattice of a crystal species, the first step in crystal formation. There are two types of nucleation: homogeneous nucleation and heterogeneous nucleation. When a solution is pure, the nucleation process is homogeneous. In human urine, though, the chemical environment is diverse, and homogeneous nucleation is unlikely to occur; rather, a heterogeneous nucleation process, by which crystal nuclei can form on structures such as cellular material, urinary crystals, and urinary casts, occurs ***(Khan, 1997).***

Aggregation:

Crystal nuclei bind to one another to form larger particles, a process known as aggregation ***(Chung et al., 2007).***

In the urinary environment, chemically or electrically induced forces can promote crystal aggregation; once crystals have aggregated to one another, they are held in place by strong intermolecular forces, and cannot be easily separated. Crystal aggregation is likely an important mechanism in stone formation, as a single crystal will never be large enough to be retained in the urinary collecting system ***(Kok et al., 1990).***

Epitaxy:

Most stones are composed of more than one crystal type, but the process by which a multicomponent stone forms is not well understood. Certainly heterogeneous nucleation accounts for the initiation of the process. However, it is likely that epitaxy, or the process by which one crystal lattice overgrows another crystal lattice, also has a contributory role. For epitaxy to occur, the crystal lattices of the constituent components must be compatible and supportive. Intermolecular forces, particularly ionic bonds, account for the strength of attachment of one lattice to another. ***(Mandel N and Mandel GS, 1990).***

Retention:

For a stone to form, crystal retention is necessary; if nucleated and aggregated crystals passed out of the renal collecting system with normal urinary flow, a clinically evident kidney stone would never form. Therefore, stone formation hinges on the retention of crystal material in the kidney until it achieves a size great enough that it is a clinical renal calculus. There have been two mechanisms proposed to account for crystal retention: the free particle hypothesis and the fixed particle hypothesis ***(Kok et al., 1994).***

It may also be that cell surface molecules, so-called crystal-binding molecules such as phosphatidylserine, sialic acid, and hyaluronan, promote this process as well ***(Yamate et al., 1999).***

Inhibitors of Crystal Formation:

1. Citrate acts as an inhibitor of calcium oxalate and calcium phosphate stone formation by a variety of actions. First, it complexes with calcium, thereby reducing the availability of ionic calcium to interact with oxalate or phosphate ***(Pak et al., 1982).*** Second, it directly inhibits the spontaneous precipitation of calcium oxalate ***(Nicar et al., 1987)*** and prevents the agglomeration of calcium oxalate crystals ***(Kok et al., 1986).*** Although it has

limited inhibitory effect on calcium oxalate crystal growth, it has potent activity in reducing calcium phosphate growth ***(Meyer et al., 1975).*** Lastly, citrate prevents heterogeneous nucleation of calcium oxalate by monosodium urate ***(Pak and Peterson, 1986).***

2. The inhibitory activity of magnesium is derived from its complexation with oxalate, which reduces ionic oxalate concentration and calcium oxalate supersaturation ***(Meyer et al., 1975).*** In addition, magnesium reduces the rate of calcium oxalate crystal growth in vitro ***(Desmars et al., 1973).***

3. Polyanions including glycosaminoglycans, acid mucopolysaccharides, and RNA have been shown to inhibit crystal nucleation and growth. Among the glycosaminoglycans, heparin sulfate interacts most strongly with calcium oxalate monohydrate crystals ***(Yamaguchi et al., 1993).***

4. Two urinary glycoproteins, nephrocalcin and Tamm-Horsfall glycoprotein are potent inhibitors of calcium oxalate monohydrate crystal aggregation ***(Mo et al., 2004).***

5. Osteopontin, or uropontin, is an acidic phosphorylated glycoprotein expressed in bone matrix and renal epithelial cells of the ascending limb of the loop of Henle and the distal tubule. Osteopontin has been shown to inhibit

nucleation, growth, and aggregation of calcium oxalate crystals, as well as to reduce binding of crystals to renal epithelial cells in vitro ***(Asplin et al., 1998).***

6. Lastly, inter-α-trypsin is a glycoprotein synthesized in the liver that is composed of three polypeptides (two heavy chains and one light chain), of which bikunin comprises the light chain. Bikunin is a strong inhibitor of calcium oxalate crystallization, aggregation, and growth in vitro ***(Atmani et al., 1999).***

Pathogenesis of upper urinary tract calculi:

Classification of Nephrolithiasis:

The most common component of urinary calculi is calcium, which is a major constituent of nearly 75% of stones. Calcium oxalate makes up about 60% of all stones; mixed calcium oxalate and hydroxyapatite, 20%; and brushite stones, 2%. Both uric acid and struvite (magnesium ammonium phosphate) stones occur approximately 10% of the time, whereas cystine stones are rare (1%) ***(Pearle and Lotan, 2012).***

Stones associated with medications and their byproducts such as triamterene, adenosine, silica, indinavir, and ephedrine are uncommon and usually preventable ***(Pearle and Pak, 1996).***

Most classification systems for nephrolithiasis differentiate stones on the basis of the underlying metabolic or environmental abnormalities with which they are associated (Table 1).

Table (1): Diagnostic classification of nephrolithiasis ***(Michael et al., 2012).***

CONDITION	METABOLIC/ENVIRONMENTAL DEFECT	PREVALENCE (%)
Absorptive hypercalciuria		20-40
Type I	Increased gastrointestinal calcium absorption	
Type II	Increased gastrointestinal calcium absorption	
Renal phosphate leak	Impaired renal phosphorus absorption	
Renal hypercalciuria	Impaired renal calcium reabsorption	5-8
Resorptive hypercalciuria	Primary hyperparathyroidism	3-5
Hyperuricosuric calcium nephrolithiasis	Dietary purine excess, uric acid overproduction	10-40
Hypocitraturic calcium nephrolithiasis		10-50
Isolated	Idiopathic	
Chronic diarrheal syndrome	Gastrointestinal alkali loss	
Distal renal tubular acidosis	Impaired renal acid excretion	
Thiazide-induced	Hypokalemia	
Hyperoxaluric calcium nephrolithiasis		2-15
Primary hyperoxaluria	Oxalate overproduction	
Dietary hyperoxaluria	Increased dietary oxalate	
Enteric hyperoxaluria	Increased intestinal oxalate absorption	
Hypomagnesiuric calcium nephrolithiasis	Decreased intestinal magnesium absorption	5-10
Gouty diathesis	Low urinary pH	15-30
Cystinuria	Impaired renal cystine reabsorption	<1
Infection stones	Infection with urease-producing bacteria	1-5
Low urine volume	Inadequate fluid intake	10-50
Miscellaneous or no abnormality	NA	<3