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Review Article

Pathophysiological aspects of renal stone formation and stone types

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Abstract

Urinary stone formation is one of the oldest and most widespread diseases known to man. The disease has a multifactorial etiology that includes anatomic, environmental, genetic, infectious, metabolic, nutritional, and most importantly socio-economic factors. It is caused by a biochemical imbalance in urine between stone-forming inhibitors and promotors in a process known as lithogenesis. The mechanisms underlying the formation and development of urinary stones are not fully understood, but it can be said that they generally begin by increased urinary supersaturation of lithiasis promoters in the urine, followed by nucleation and aggregation. Subsequently, the crystals combine with other crystals in solution to form agglomerates that accumulate in the kidney. Free radical-mediated oxalate-induced renal membrane damage promotes crystal retention at the surface of the renal papilla, as well as crystal nucleation at lower supersaturation levels. In addition, stone type identification is of great interest in guiding the physician to an effective diagnosis, which allows to determine the causes in order to treat the disease and prevent recurrence. In this context, this present study reviews current knowledge on the pathophysiological aspects of kidney stone formation as well as the type of stones.

Keywords: kidney stone disease; pathophysiological aspects; stone formation; stones type

Introduction

Kidney stone disease is a crystalline concretion of mineral and organic components formed in the kidneys or in the urinary tract. About 80% of kidney stones contain calcium oxalate (CaOx) as the main mineral phase, mainly mixed with calcium phosphate (CaP) and sometimes uric acid (Khan, 2014). Urolithiasis represents a growing urological disorder of human health, affecting approximately about 2 to 20% of the population, with variations observed across different countries (Hesse *et al.*, 2003). According to estimates, within the first 5 years following the discovery of the first stone, the likelihood of recurrence ranges between 30 to 50%, while in the subsequent 10 years, the rate increases to approximately 50 to 60% (Curhan, 2007; Safarinejad, 2007; Daudon, 2008; Arumuham and Bycroft, 2016). This pathology has been recognized

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since the earliest times and is an integral part of the human history (El Lekhlifi *et al*., 2014). The archaeological and paleontological documents clearly show that this pathology is one of the oldest human diseases. The first documented urinary and bladder stones were identified by Shattock in 1905 (Modlin, 1980), found in Egyptian mummies and dated to about 4400 BC. -JC for the first stone and from 4800 BC. -JC for the second (Modlin, 1980).

The urolithiasis management involves drug treatments and/or surgical intervention to extract the stones by the techniques such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), percutaneous nephrolithotomy (PCNL) and open surgery. This latter becoming relatively uncommon, although there is some use laparoscopic/robotic surgery for stone removal (Geraghty *et al*., 2017, 2023). Moreover, endoscopic stone removal and ESWL have revolutionized the treatment of urolithiasis, this latter technique show a success rate for kidney stones with minimum complications rate, but depend on the stone's characteristics, patient and other parameters (Chakit *et al*., 2023). The use of URS has increase over the past decade due to massive innovations in minimally invasive surgery and recommended for intra-renal stones of 1-2 cm (Geraghty *et al*., 2017). On the other hand, these methods are expensive and can cause acute kidney injury and decline in kidney function, moreover, do not prevent the likelihood of new stones formation (Agawane *et al*., 2019; Sikarwar *et al*., 2017).

However, various therapies, including thiazide diuretics and alkaline citrate, are used in an attempt to prevent the recurrence of stones induced by hypercalciuria and hyperoxaluria, but the scientific evidence for their effectiveness is less convincing (Bashir and Gilani, 2011; Sikarwar *et al*., 2017). Currently, there is no satisfactory drug to cure and/or prevent the recurrence of kidney stones, which remains a serious health problem for humans (Alelign and Petros, 2018). Therefore, a better understanding of the mechanisms involved in the formation of stones is a necessity for prevention and the development of treatment methods. In this context, this work provides a synthesis on the pathogenesis and pathophysiological aspects of urolithiasis, as well as the type of stones.

The pathogenesis of kidney stone disease is a very complicated phenomenon that implies physiological, physicochemical, biological, biochemical and genetic aspects that act individually or in synergy. It is important to note that there are not many studies that investigate and examine all these variables together.

Pathogenesis and physiopathology of urolithiasis

Stone formation brings together all biological and physicochemical processes that occur from supersaturated urine and lead to the formation of a stone in the urinary tract. This process is called "lithogenesis" and involves several phases that occur sequentially or simultaneously (Figure 1) (Daudon *et al*., 2008; Aggarwal *et al*., 2013).

These phases can be classified into two stages. The first one concerns certain initial phases of lithogenesis, which may be called crystallogenesis. It's corresponds to the formation of crystals from substances initially dissolved in the urine and is not in itself a pathological process (Daudon *et al*., 2008). While the second stage includes the retention and development of stones in the urinary tract, known as calculogenesis. However, understanding the lithogenesis mechanisms involved in the formation of each stone is an essential step in defining effective rules for treatment and recurrence prevention (Daudon *et al*., 2000, 2008).

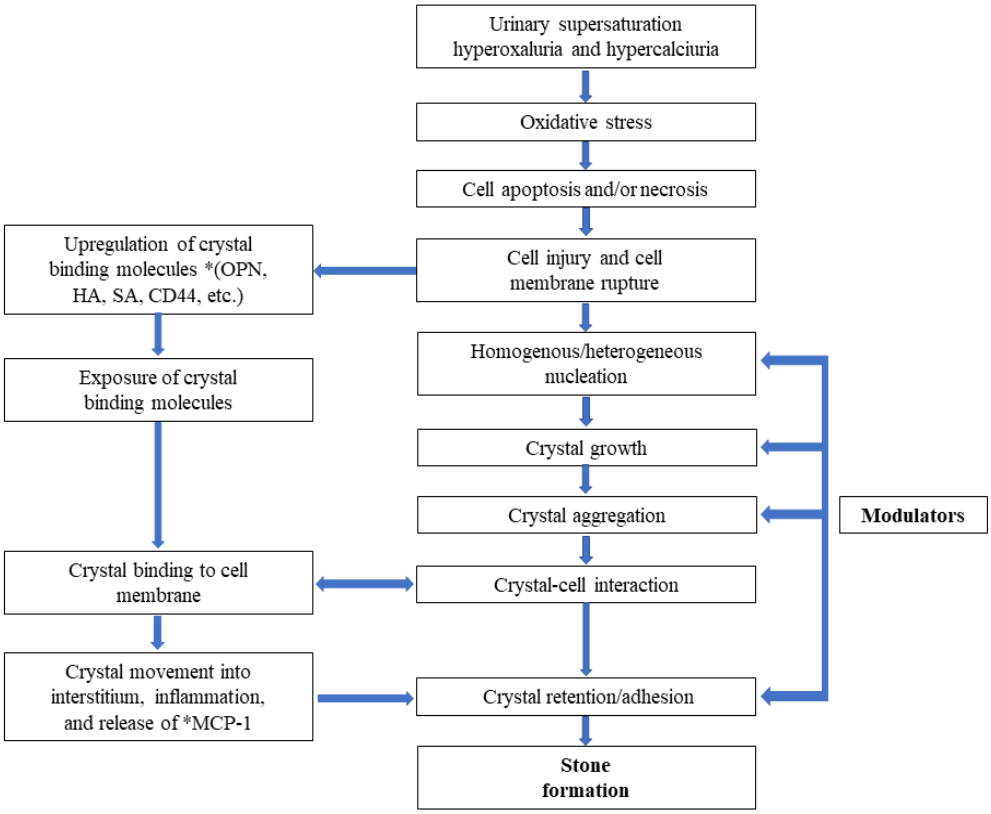

Figure 1. Schematic representation of various cellular and extracellular events during urinary stone formation. (OPN: osteopontin, HA: hyaluronic acid, SA: sialic acid, MCP-1: monocytic chemotactic protein-1.) (Aggarwal *et al*., 2013)

Several possible hypothetical models have been proposed to explain the mechanism of urinary stone initiation and formation. No single model can rationalize the evidence observed in all patients with this disease, as many factors can interfere (Khan *et al*., 2016). Nevertheless, the chemical processes of crystal nucleation and growth are essential for the initiation and development of all stone's types (Robertson *et al*., 1971). However, stone formation is caused by an abnormal combination of factors affecting the thermodynamic driving force (supersaturation) and kinetic processes (flow control), involved in the crystallization of various minerals (Khan *et al*., 2016).

Urine supersaturation

In solutions like urine, the process of crystallisation is primarily driven by supersaturation. As a simple definition, upon addition of a salt to a solvent, it will dissolve until it reaches a certain concentration, at which point no further dissolution is possible. This concentration is known as the saturation point. An additional dose of salt will lead to crystallization as long as the temperature, pressure and pH remain unchanged (Aggarwal *et al*., 2013). Indeed, in the living environment, the latter parameter (pH) is the most important factor influencing the solubility of the substance, as the pressure and temperature can be considered constant (Daudon *et al*., 2008). In the majority of individuals, urine is almost always metastable to calcium oxalate, whether they develop stones or not. Additionally, at certain times, it may also be metastable to other components, such as uric acid, urates and calcium phosphate. Although the urine of patients with calcium is often more supersaturated with calcium oxalate and calcium phosphate than in normal individuals. Nevertheless, even in this case (supersaturation), nucleation of calcium oxalate, or phosphates does not usually

occur, and the crystals produced do not grow and aggregate to a sufficient size to be retained in the kidney on the basis of size alone (Kok and Khan, 1994). This result is probably due to the presence of crystal formation inhibitors, particularly during the nucleation, growth or aggregation stage (Ratkalkar and Kleinman, 2011; Verkoelen, 2006).

Supersaturation (SS) is expressed as the ratio between the solute's concentration (C) and its solubility product (Miller *et al*., 2007; Ratkalkar and Kleinman, 2011). The point at which saturation of a solution is reached and crystallisation begins, is commonly referred to as the thermodynamic solubility product (Ksp) (Figure 2). Subsequently, as the concentration of the solute continues to increases, it eventually reaches a level where it exceeds the maximum solubility and can no longer remain dissolved. At this point, crystals begin to form in the urine, which is called the formation product (Kf) (Basavaraj *et al*., 2007). On the other hand, if crystallisation inhibitors were unable to act, the end result would be nephrolithiasis (Carvahlo and Nakagawa, 1999; Miller *et al*., 2007; Ratkalkar and Kleinman, 2011; Aggarwal *et al*., 2013).

At SS values less than 1, the crystals of a substance dissolve, whereas, at SS values greater than 1, crystals can form and develop. Although increasing urine volume is an obvious way to reduce SS. In addition, and for unclear reasons, Coe *et al*. (2005) found that sodium intake and urinary calcium excretion increased with increasing urine volume, partially offsetting the drop in SS. However, the most important determinants for calcium oxalate (CaOx) SS are urine calcium and oxalate concentrations, whereas for calcium phosphate (CaP), urine calcium concentration and pH are crucial. The latter parameter also represents a primary determinant of uric acid (UA) SS (Coe *et al*., 2005).

The SS range between the solubility product and the point of crystal formation (Kf), is called the metastable zone (Figure 2), where the concentration of the salt is greater than its solubility and precipitation is inevitable. The amount of salt required to produce a solid phase is called the upper limit of metastability (ULM) (Coe *et al*., 2005; Miller *et al*., 2007).

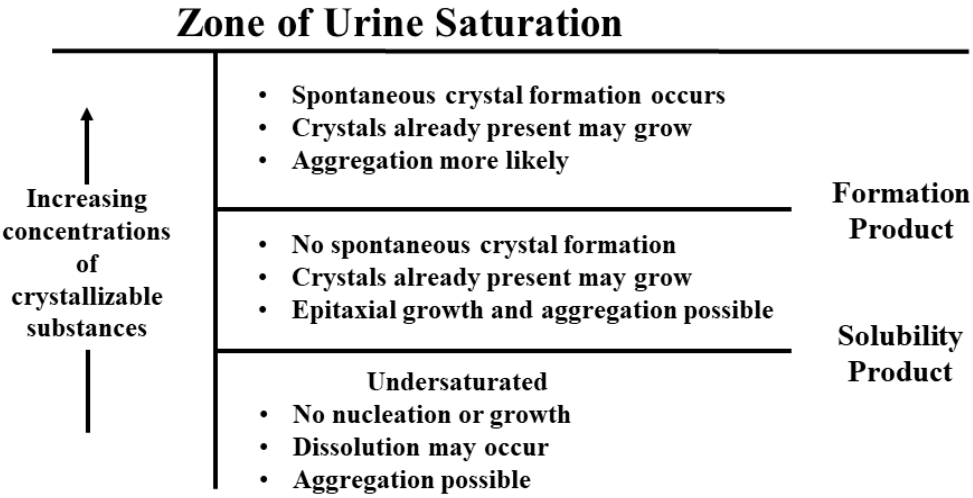

Figure 2. Saturation states of a solution (Miller *et al*., 2007)

When SS exceeds Kf, the urine enters an unstable zone. Due to the high level of supersaturation, the kinetics of crystallization enable the formation and growth of crystals, will allow the formation and growth of crystals in the time necessary for the urine transit through the kidney. Knowing that the transit time of urine through the nephrons during usual diuresis is between 1 and 3 minutes (Daudon *et al*., 2000). When the urine is below the Kps for a particular solute, this latter cannot crystallise.

Crystalline germination-nucleation

Nucleation is the initial process of crystallisation, in which occurs at a critical level of SS, the reunion of a small number of molecules (a few tens or hundreds) to form a crystal nucleus, which can then grow by subsequent deposition from the solution. This is called primary nucleation when the crystals of the precipitation phase are not involved, or secondary nucleation when nuclei form on pre-existing crystal surfaces. Primary nucleation can be divided into homogeneous and heterogeneous nucleation (Kavanagh, 2011). Homogeneous nucleation occurs spontaneously when the supersaturation is sufficient. This is difficult to achieve in practice as all foreign particles and surface defects must be excluded. Nucleation that occurs on an existing surface, such as cell membranes, cell debris, other crystals, red blood cells, and urine streams is called heterogeneous. The latter occurs at a lower SS level than homogeneous nucleation (Miller *et al*., 2007; Kavanagh, 2011; Aggarwal *et al*., 2013; Alelign and Petros, 2018).

Damage to renal tubule cells can favour the crystallisation of CaOx crystals by providing substances for their heterogeneous nucleation (Khan, 2006; Aggarwal *et al*., 2013). *In vitro* cellular degradation subsequent to renal tubular cells injury produces numerous membrane vesicles, that have been observed to serve as effective nucleators of calcium crystals, including CaP and CaOx. Indeed, incubation of the proximal tubular border membrane in a metastable solution of calcium oxalate shows the association of the latter with cellular degradation products (Khan *et al*., 1990; Fasano and Khan, 2001). However, the stone matrix contains both membrane vesicles and lipids, cell membrane phospholipids are proposed to promote crystal nucleation (Khan *et al*., 2002). It is interesting to note that the damaged but intact membranes cells also showed the ability of CaOx crystals to nucleate. Direct nucleation on the cell surface may also promote crystal retention in the tubule (Lieske and Deganello, 1999).

On the other hand, oxalate is widely distributed in plant-based foods as potassium, sodium and ammonium oxalate (water soluble form) and insoluble calcium oxalate. Oxalate has been shown to be toxic to renal epithelial cells of cortical origin. It has been observed that exposure of renal epithelial cells to oxalate results in disruption of normal renal epithelial activities (Aggarwal *et al*., 2010), alterations in gene expression (Khan *et al*., 2014), impaired mitochondrial function (Cao *et al*., 2004), formation of reactive oxygen species (ROS) (Thamilselvan *et al*., 2003; Yu *et al*., 2011) and consequently a decrease in cell viability (Aggarwal *et al*., 2010). Oxalate-induced membrane damage is mediated by peroxidation of lipids and proteins via ROS generation with altered biochemical reactions, including depletion of the antioxidant defense system and the calcium pump failure. Calcium and oxalate accumulate and then precipitate in the presence of membrane fragments to form stones (Khan, 2005; Ahmed *et al*., 2018).

According to Khan's research in 2004, the interaction between kidney cells and crystals leads to the generation of reactive oxygen species (ROS), which in turn cause diverse cellular responses (Khan, 2004). However, crystals deposition is a relatively common phenomenon in the kidneys and often associated with inflammation. Calcium phosphate (CaP) and calcium oxalate (CaOx) crystals can cause tubulointerstitial damage and inflammation. Urate crystals associated with chronic gout cause an intense inflammatory reaction. Cystine crystals in homozygous cystinuria patients also trigger an inflammatory response (Khan, 2004).

Furthermore, exposure of renal epithelial cell to crystals leads to increased synthesis of osteopontin (OPN), bikunin, heparin sulfate, monocyte chemoattractant protein 1 (MCP-1) and prostaglandin E2. These compounds are known for their participation in inflammatory processes and in extracellular matrix production. This exposure also results in a significant increase in the release of lactate dehydrogenase (LDH) (cell injury indicator) and cellular malondialdehyde (MDA) content (lipid peroxidation indicator) (Thamilselvan *et al*., 2003). The deposition of calcium oxalate crystals in the kidneys of rats also activates the renin-angiotensin system (Khan, 2004). In parallel, *in vitro* pretreatment of renal epithelial cells with Diphenyleneiodium (DPI) (NADPH oxidase inhibitor), leads not only to a reduction in ROS, MCP-1 and OPN production, but also to a reduction in cell damage induced by oxalate and calcium oxalate crystals (Umekawa *et al*., 2005). Vitamin E effectively restores cellular antioxidants and prevents lipid peroxidation

(Thamilselvan *et al.*, 2003). In addition, citrate and vitamin E reduce free radicals production induced by shock wave lithotripsy treatment (Delvecchio *et al.*, 2005). The study by Umekawa *et al.* (2004) reported that the kidneys of hyperoxaluric rats treated with candesartan, an angiotensin II type I receptor inhibitor, had less crystalline calcium oxalate deposits, reduced OPN expression, and lower MDA levels compared to untreated rats (Umekawa *et al.*, 2004).

Concerning the mechanism of action (Figure 3), calcium oxalate crystals adhere to epithelial cells and NADPH oxidase generates superoxide ($O2^{\bullet-}$), which will activate cyclophilin D. The opening of the mitochondrial permeability transition pore (mPTP) associated with mitochondria collapse, generates oxidative stress, activation of the apoptotic pathway and a high OPN expression. In contrast, cyclosporin A and N-methyl-4-isoleucine cyclosporine (NIM811), a novel selective inhibitor of cyclophilin D activation, blocks mPTP opening by inactivating cyclophilin D, OPN expression and renal calcification (Niimi *et al.*, 2012; 2014, Yasui *et al.*, 2017).

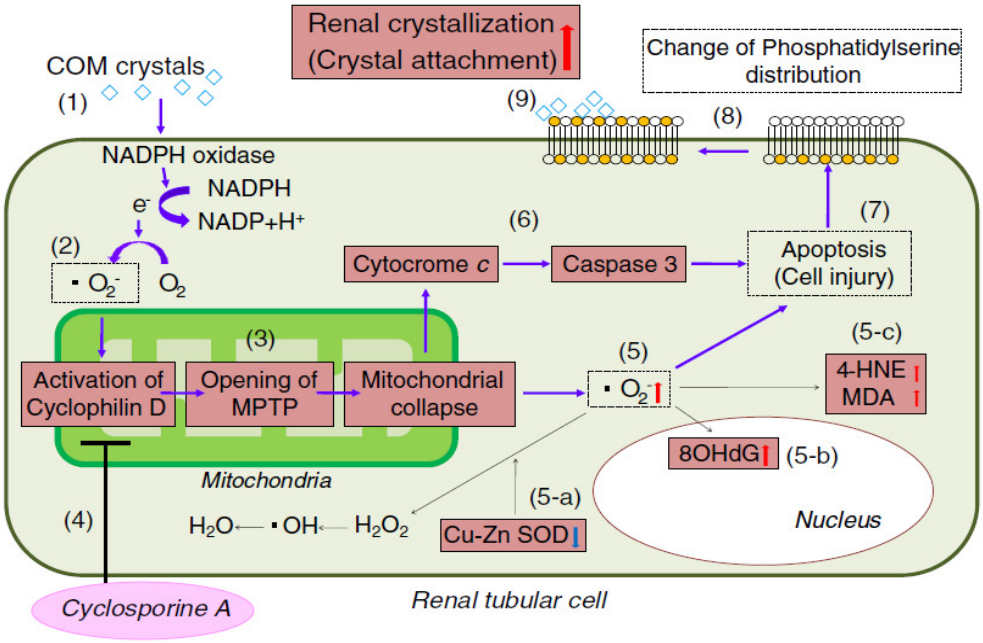

Figure 3. Proposed pathway for the explanation of renal epithelial cell exposure to crystals: (1) COM crystals attach to renal tubular cells; (2) NADPH oxidase generates $O2^{\bullet-}$; (3) cyclophilin D activation and mPTP opening accompanied by mitochondrial collapse; (4) blocking of mPTP opening through inactivation of cyclophilin D by cyclosporin A (5) $O2^{\bullet-}$ release by mitochondria; (5-a) decrease in SOD; (5-b) increase in 8-OHdG, (5-c) increase in 4-HNE and MDA; (6) cytochrome C release by mitochondria, caspase 3 activation; (7) apoptosis activation and cell damage (8) modification of phosphididylserine distribution in renal tubular cells membranes; (9) increased crystal binding and crystallization (Niimi *et al.*, 2012)

Cytochrome C, an important apoptosis-inducing protein, that is also released during mitochondrial collapse, thereby activating caspase-9 and caspase-3. These events trigger the onset of apoptosis, cell injury and alter the phosphatylserine distribution in renal tubular cells membranes (Kohri *et al.*, 2012; Niimi *et al.*, 2012). However, during this process, ROS are also released from the intramembrane compartment into the cytosol, further damaging the renal tubular cells (Yasui *et al.*, 2017).

Crystal growth

Once a crystal nucleus reaches a critical size and the relative supersaturation remains greater than 1, the overall free energy is reduced by adding new crystalline components to the nucleus (Aggarwal *et al*., 2013). However, crystal growth is determined by molecule size and shape, material physical properties, SS levels, pH, and any defects that may form in the crystal structure (Basavaraj *et al*., 2007). Furthermore, the process of stone growth is slow and takes time, often longer than the transit time of urine through the nephron, making the risk of intra-renal crystalline retention by crystals size very low (Daudon *et al*., 2008).

Crystals aggregation-agglomeration

Aggregation is a crucial step in stone formation, where the crystals in solution stick together to form larger particles. In this process, large particles (several tens or, more rarely, several hundred microns) are formed in a very short time, less than the passage time of urine through the kidney (Daudon *et al*., 2008; Tsujihata, 2008; Alelign and Petros, 2018). However, the phenomenon of electrostatic attraction as a function of crystal surface charge has been implicated to explain this action (Miller *et al*., 2007; Daudon *et al*., 2008). Crystal agglomeration is favoured by viscous bonds, involving urinary macromolecules (lipids, polysaccharides, and other materials derived from cells), which have several binding sites and act as a kind of glue. The latter secondarily promotes the attachment of new crystals to the former by relating them to each other, contributing to stone architecture and thus leading to retention of particles in the urinary tract (Basavaraj *et al*., 2007; Miller *et al*., 2007; Daudon *et al*., 2008; Ratkalkar and Kleinman, 2011; Aggarwal *et al*., 2013). Yet, the interactions between macromolecules and crystals are complex and depend on several factors such as pH, ionic strength, inhibitors and promoter's concentration. All of these factors can alter the conformation of these macromolecules, their affinity for crystals and their efficiency in exerting their inhibitory action (Daudon *et al*., 2008).

Crystal retention

Stone's development needs crystals formation in the tubular fluid, followed by crystals retention and accumulation in the kidneys (Verkoelen and Verhulst, 2007). Three pathways of stone formation and growth have been proposed by Evan (2010) (Figure 4B). The first hypothesis, called the free particle model, indicates that crystal nuclei are formed by homogeneous nucleation in the nephron lumen, under conditions of increasing supersaturation of salts in the ultrafiltrate. As the nuclei grow, they become lodged in the distal nephron's lumen, leading to tubular segment obstruction. The minor calyx of the renal collecting system could be the site of the free particles formation (Evan, 2010).

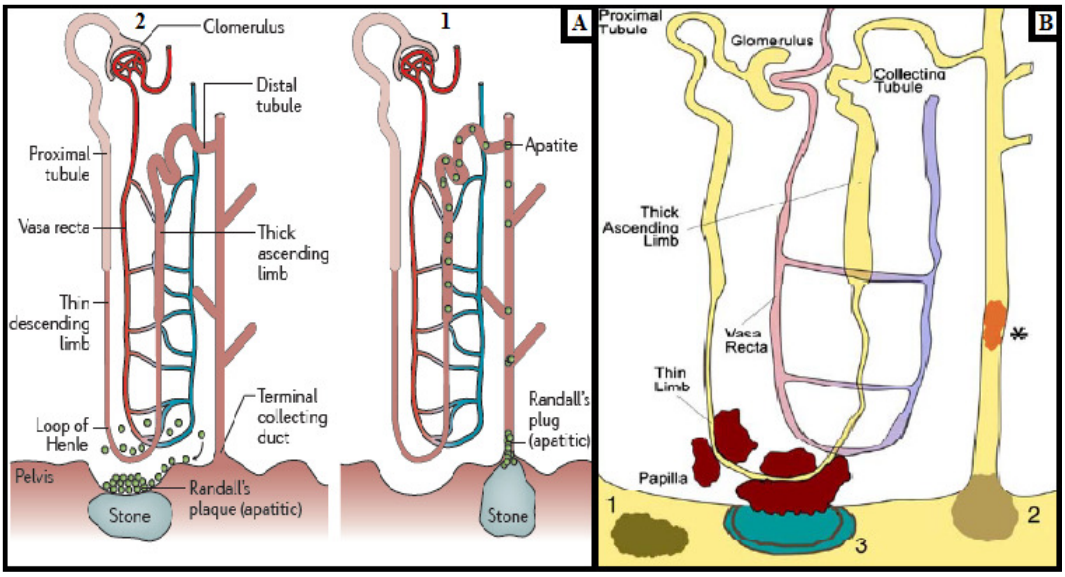

Figure 4. Illustration of crystal retention pathways: A) according to (Khan *et al.*, 2016) [1: free particle mechanism (Randall's plug); 2: fixed particle mechanism (Randall's plate)]. B) according to (Evan, 2010) [1: free particle mechanism; 2: fixed particle mechanism; 3: Randall's plaque]

The second hypothesis, called the Fixed particle model, where crystal nuclei form in the nephron lumen and then adhere to the apical surface of the tubular epithelium. Once the step of crystal attachment to the cells has occurred, the nuclei would be fixed in position and exposed to the potentially supersaturated ultrafiltrate, which would facilitate the growth of these crystals (Evan, 2010). The third pathway suggests that crystals in urine may become fixed to a site of interstitial calcium phosphate crystalline deposition (Randall's plaque), following the loss of normal urothelial coverage of a renal papilla (Figure 4B). An anchored nest of urinary crystals could form an overgrowth on the interstitial plaque, thus allowing the fixed stone to develop (Evan, 2010). However, Khan *et al.* (2016) suggest two pathways (Figure 4A) and combine the first two pathways mentioned above by (Evan, 2010) into the free particle mechanism (Randall's plug), while the second is of fixed particle (Randall's plaque) (Khan *et al.*, 2016).

Stone growth

Stone growth velocity initiated by crystal retention is very variable and depends on the urine supersaturation level, and hence on the nature of the metabolic, genetic abnormalities and dietary faults. Growth is not the only spontaneous mode of evolution that a stone retained in the urinary tract can undergo. In fact, other phenomena can also occur that lead to changes in the crystalline phases. They result from the instability of some hydrated forms which tend to evolve progressively over time towards thermodynamically more stable and less hydrated forms (Daudon *et al.*, 2008).

Stone formation promoters and inhibitors.

Inhibitors are substances that decrease the initiation of supersaturation, nucleation, crystal growth, aggregation velocity or any other process necessary for stone formation (Basavaraj *et al.*, 2007). Inhibitors can act either directly by binding to the crystal surface and preventing crystal development, or indirectly by acting on the urinary environment (Alelign and Petros, 2018). There are at least four types of inhibitors in urine (Table 1). Small organic and inorganic anions such as citrate and pyrophosphates, multivalent metal cations such as magnesium and macromolecules such as osteopontin and Tamm-Horsfall protein (Basavaraj *et al.*, 2007; Ratkalkar and Kleinman, 2011; Alelign and Petros, 2018). Some inhibitors may play two opposing roles.

They inhibit one stage of crystal formation while also promoting another stage. For example, Tamm-Horsfall Protein and glycosaminoglycans promote crystal nucleation, but inhibit crystal aggregation and growth (Miller *et al*., 2007).

Table 1. Inhibitors and promoters of crystallisation (Basavaraj *et al*., 2007; Miller *et al*., 2007; Daudon *et al*., 2008; Ratkalkar and Kleinman, 2011; Aggarwal *et al*., 2013; Alelign and Petros, 2018)

Low molecular weight inhibitors	Macromolecular inhibitors	Promoters
Cations	**Protein**	Calcium
Zn^{2+}	Tamm-Horsfall Protein	Sodium
Fe^{3+}	Nephrocalcin	Oxalate
Mg^{2+}	Uropontin/Osteopontin	Urate
Anions	Bikunin	Ammonium
Citrate	Urinary prothrombin fragment 1	Cystine
Isocitrate	Fibronectin	Tamm-Horsfall protein
Phosphocitrate	Calprotectin	Low urine pH
Pyrophosphate	Lithostathine	Low urine flow
Aspartate	Inter-a-Inhibitor	Xanthine
Glutamate	Glycosaminoglycans	Myeloperoxidase
Hippurate	Chondroitin sulphate	Albumin
	Heparin sulphate	Annexin II
	Keratan sulfate	Hyaluronic acid
	Dermatan sulfate	
	Hyaluronic acid	

However, the promoters participate in the formation of insoluble species in urine and reduce the formation product of the supersaturated solution. This product may also be reduced due to the absence of endogenous inhibitors or by their opposite effects as a result of structural defects or other interfering substances (Basavaraj *et al*., 2007; Ratkalkar and Kleinman, 2011). They are around ten in number (Table 1) and very often associate in pairs or in threes to form a crystallizable substance, which itself can be present in several crystalline species (Daudon *et al*., 2008).

Stone's type

The identification of stone type has a major interest in guiding the physician towards an accurate diagnosis, which allows to determine the causes in order to treat and prevent recurrence of the disease. For these reasons, a morpho-constitutional analysis should be performed at least once during the lithiasis history and repeated in the event of recurrence, as the causes may change (Courbebaisse *et al*., 2017). This analysis allows us to determine the chemical composition, the crystalline form as well as the stone structural characteristics. These data reveal the specific disease causes. For example, calcium oxalate stones, which are dominated by dihydrate form called weddellite, are essentially linked to hypercalciuria contexts, while those composed mainly of the monohydrate form known as whewellite are associated with hyperoxaluria, and alterations in stone structure reflect the severity of this condition (Daudon *et al*., 2008).

According to Cotton *et al*. (2014), more than 70 of the chemical species have been identified in the composition of urinary stones and may be mineral or organic, including at least 25 of drug origin (Cotton *et al*., 2014). Moreover, there are six basic morpho-constitutional categories of urinary stones that can be further split into a variety of morphological subtypes, each corresponding to a particular etiological or pathophysiological condition (Daudon *et al*., 2016a).

Oxalo-calcic stones

Globally, oxalo-calcic stones are the most frequent in the world and Morocco country. According to studies carried out in the region of Fez (Morocco), the percentage of these stones is 60.98% (El Habbani *et al*., 2016) and 56.25% in children (El Lekhlifi *et al*., 2016). 66.6% in the Rabat-Salé (Morocco) (Bouatia *et al*., 2015) and 58.5% in the Middle Atlas (Oussama *et al*., 2000). Regarding the stone's structure, there two principal types, namely calcium oxalate monohydrate (COM) (Figure 5A), that can be further categorized into five different morphological aspects (subtype types Ia, Ib , Ic, Id and Ie) and characterised by a compact structure, hard and resistant to extracorporeal shock wave lithotripsy (Doré, 2005). While the second type which is calcium oxalate dihydrate or weddellite (COD) (Figure 5B), exhibits 3 subtypes (IIa, IIb, IIc) (Doré, 2005; Lechevallier *et al*., 2008; Aguilar-Ruiz *et al*., 2012; Castiglione *et al*., 2015; Daudon *et al*., 2016a). However, calcium oxalate crystals are mainly found in three different forms which are COM, COD and the trihydrate form called caoxite (COT). The latter form is very rare (Daudon, 2013, 2015, 2016b). Yet COM is the most thermodynamically stable form, has a higher affinity for renal tubular cells, and therefore responsible for stones formation in kidney (Verkoelen *et al*., 1995; Wesson *et al*., 1998).

Phosphate stones

These stones type can be divided into two major groups which are calcium phosphates and ammonium magnesium phosphates. The most well-known are brushite (Figure 5G), carbapatite (Figure 5E) and struvite (Figure 5F). The latter two are associated with a chronic urinary tract infection by urease-positive bacteria (*Proteus, Klebsiella pneumoniae, Pseudomonas aeruginosa Staphylococcu saureus, aspergillus fumigatus, Enterobacters*). The latter produce the urease which is necessary to cleave urea into ammonia and CO_2, making the urine more alkaline at a pH generally higher than 7 and promotes their precipitation in insoluble ammonium-based products. This stone type is also called coralliform stones, because it can grow rapidly and fill pyelocalicial cavities (Puigvert, 2002; Rieu, 2005; Bruyere *et al*., 2008).

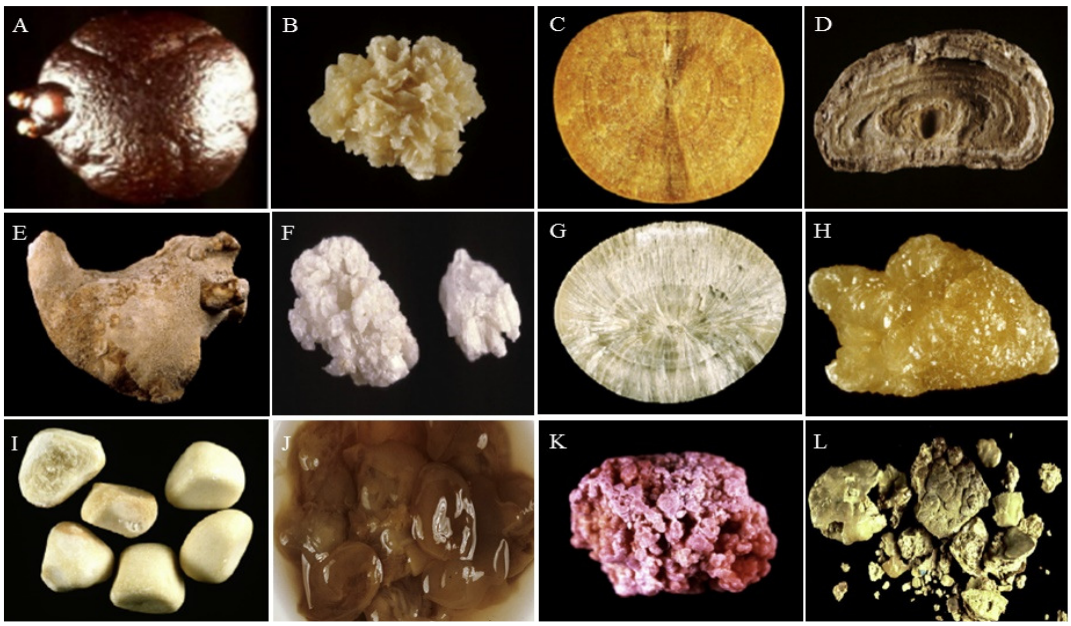

Figure 5. Different types of urinary stones: A) Calcium Oxalate Monohydrate; B) Calcium Oxalate Dihydrate; C) Anhydrous Uric Acid; D) Ammonium Urate; E) Carbapatite; F) Struvite; G) Brushite; H and I) Cystine; J) Protein; K) N-acetylsulfadiazine; L) Metabolites triamterene (Cloutier *et al*., 2015; Daudon *et al*., 2016a; Estrade *et al*., 2017).

Uric stone

Uric stones have a high frequency in Morocco with percentages of 19.8 and 18.42% in the regions of Rabat and Fez respectively (Bouatia *et al*., 2015; El Habbani et al., 2016). Diets rich in purines, especially those containing animal protein, such as meat and fish, lead to hyperuricosuria, low urine volume, and low urine pH below 5.05, which promotes the uric acid stone formation (Figure 5C; D) (Alelign and Petros, 2018). In contrast, the alkalisation of urine by bicarbonate intake converts uric acid, which is very poorly soluble in ionized form, into very soluble urates. Moreover, a low-fructose diet (such as sodas, fruit juices, honey, maple syrup, etc.) and in purines (offal, game, poultry, cold meats, anchovies, crustaceans, etc.) must be provided to reduce the risk formation of this stones type.

Cystine stones

Cystine stones are uncommon and result from an abnormal transport of dibasic amino acids in the proximal tube. This hereditary disorder with autosomal recessive or incompletely recessive transmission depending on the genetic form, results in urine leakage of these amino acids, of which cystine is the least soluble. This leads to intratubular cystine crystallisation in the excretory tract (Traxer *et al*., 2008). Cystine stone (Figure 5H; I) is hard and more resistant to ESWL, producing large blocks that can obstruct the excretory tract (Doré, 2005). Its medico-surgical management is essential to limit the risk of lithiasis recurrence and to preserve the patient's renal function (Traxer *et al*., 2008).

Drug-induced stones

Drug stones are rare and can be classified into two categories. The first is the result of a drug's urinary crystallisation, or a poorly soluble metabolite whose urinary excretion is important. The second includes all those related to the drugs metabolic effects. This type of stone appears in patients treated with a high dose and long term, and by the intervention of other factors such as urine pH, diuresis (Servais *et al*., 2006).

Protein stones

Stones composed principally of protein are infrequent. They can be found mainly in three clinical settings. The first is chronic pyelonephritis linked to a urinary tract infection, the second concerns proteinuria observed in glomerular kidney disease, hematuria where bleeding caused by crystals and the third corresponds to the situation of end-stage renal disease (Daudon *et al*., 2016a).

Conclusions

This review work has highlighted the process of urinary stone formation, which includes all the biological and physicochemical pathways produced from supersaturated urine and lead to the development of a stone in the urinary tract. The studies on this process must be deepened because many aspects of the kidney stones formation remain unclear and sometimes contradictory. This will lead to the development of a new prevention strategy, as well as the development of drugs against this disease.

Authors' Contributions

RK: Conceptualization, wrote the paper, collect and interpret data; GBT, GEM, REH, MM and AL: Contribution to writing the manuscript, correction of the final manuscript. All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

Not applicable.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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