INTRODUCTION

Staghorn calculi are large branched stones that fill all or part of the renal pelvis and extended into the majority of the renal calices. While "staghorn" describes configuration rather than composition, most staghorn stones consist of pure magnesium ammonium phosphate (struvite) or a mixture of struvite and calcium carbonate apetite. These stones are also referred to as infection stones because of their strong association with urinary tract infection caused by urea splitting organisms.

Stones composed of uric acid or cystine may also grow in a staghorn configuration ***(Cranidis, 1996),*** but this branched pattern of stone is rare with calcium oxalate or phosphate stone.

If left untreated, staghorn calculi may lead to deterioration of renal function, end stage renal disease and life threatening urosepsis since the stones often remain infected ***(Preminger et al., 2005).***

The management of complete staghorn stones remains one of the difficult tasks for the urologist. Complete removal of the stone is the primary treatment goal in order to relieve obstruction, eliminate infection, prevent further stone growth and preserve renal function ***(Preminger et al., 2005).***

Open surgical procedures such as extended pyelolithotomy and anatrophic nephrolithotomy remained unchallenged until the introduction of percutenous nephrolithotomy (P.N.L) as an acceptable method of treatment of staghorn stones ***(Alken et al., 1981).***

Subsequently with the introduction of shock wave lithotripsy (S.W.L.) it became popular to combine P.N.L. and S.W.L. in treating such stones ***(Segura et al., 1987).***

Retrograde endoscopic lithotripsy is also one of the treatment options in selected cases ***(Marguet et al., 2005).***

Nephrectomy is a reasonable option for a patient with a staghorn stones in a non functioning or poor functioning kidney with normal contralateral kidney.

The procedure or combination of procedures most likely to render the patient free of stone material with the lowest morbidity should be selected.

AIM OF THE ESSAY

Because of the treatment recommendations of staghorn stones are highly variable, we will review the literature to determine the optimal treatment of staghorn stones in different situations to achieve complete clearance of the stone burden with minimal morbidity, namely, fewer complications, shorter hospital stay and lower blood transfusion requirements. And also to compare the different treatment options as regard to effectiveness and complications.

Chapter (1)

PATHOGENESIS OF STAGHORN CALCULI

Most staghorn stones consist of pure magnesium ammonium phosphate or a mixture of magnesium ammonium phosphate and calcium carbonate apetite.These stones are also referred to as infection stones because of their strong association with urinary tract infection caused by urea splitting organisms.

A branched pattern of stone growth may also occur with cystine and uric acid stones, but is rare with calcium oxalate stones ***(Cranidis, 1996).***

1- Pathogenesis of infection stones as the commonest cause of staghorn calculi

In 1845, a Swedish geologist named Ulex discovered magnesium ammonium phosphate in bat guano and named the substance ‘‘struvite’’ after his mentor, the Russian diplomat Baron H.C.G. von Struve.

Struvite calculi are typically referred to as infection stones because of their strong association with urinary tract infections with urease producing bacteria. The most important

urease producers include Proteus, Klebsiella, Pseudomonas, and Staphylococcus species (***Heimbach et al., 2002***).

However, the most ubiquitous uropathogen, Escherichia coli, only rarely produces urease and thus is an infrequent cause of staghorn calculi (***Rahman et al., 2003).***

Infection stones are characterized by their large size and exceptionally rapid growth. In fact, 4 to 6 weeks may be sufficient time for an infection stone to form and subsequently develop into a staghorn stone that involves the entire renal pelvis and calices (***Bichler et al., 2002)*.**

Most commonly, staghorn stones are composed of a mixture of struvite (magnesium ammonium phosphate) and calcium carbonate apatite. Normal urine is undersaturated with ammonium phosphate, and struvite stones only form when ammonia production is elevated and urine pH is increased, thereby decreasing the solubility of phosphate (***Hesse and Heimbach, 1999***). This occurs when urinary tract infection with a urease-producing organism is present (Fig. 1) ***(Bichler et al., 2002)*.**

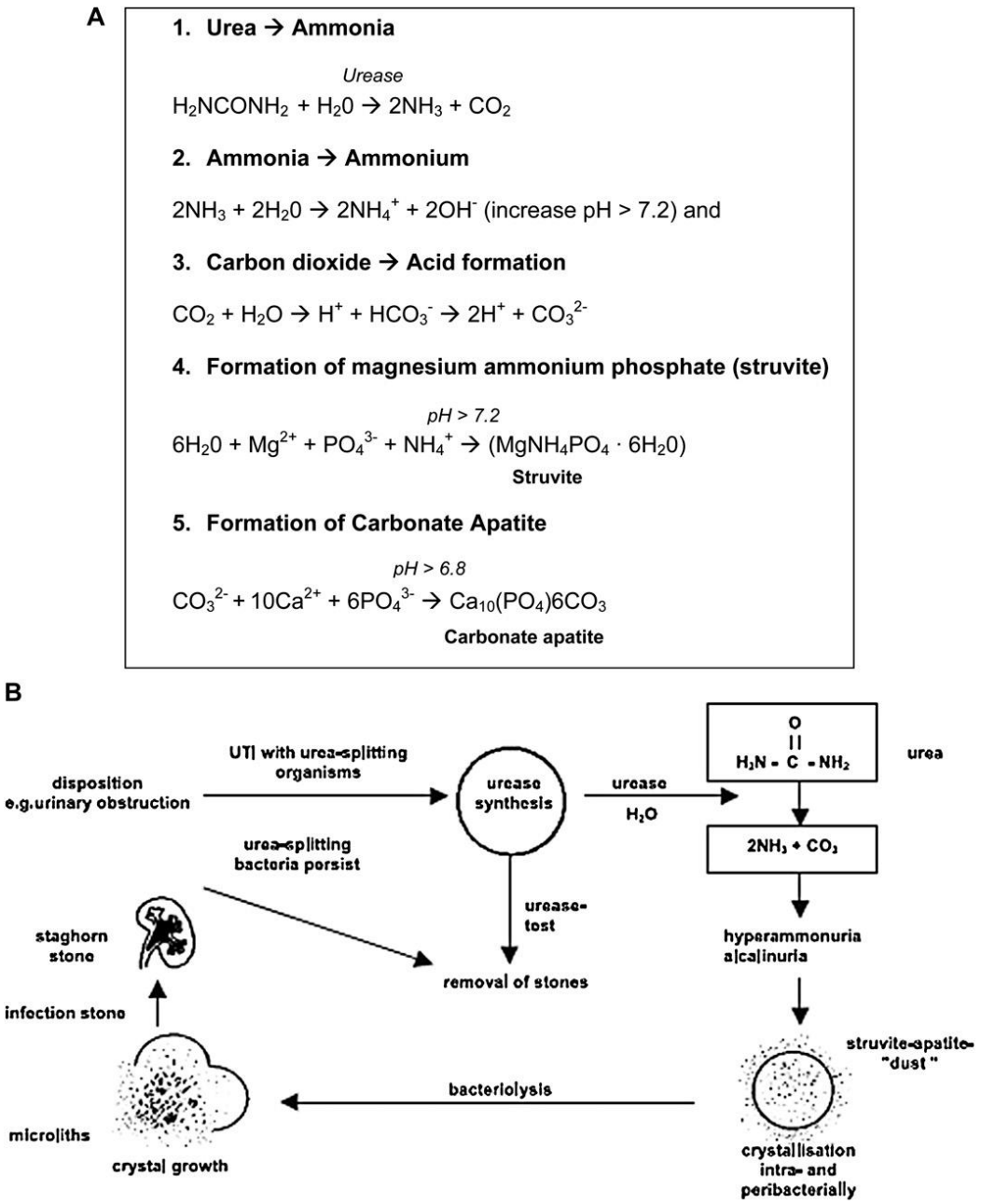

Fig. (1): (A) Pathogenesis of struvite–carbonate-apatite stone formation. (B) Pathogenesis of infection stone. UTI, urinary tract infection. (B adapted from Bichler KH, Eipper E, Nabor K, et al. Urinary infection stones. Int J Antimicrob Agents 2002;19(6):491; with permission from the American Chemical Society).

First, bacteria-produced urease breaks down urinary urea into ammonia plus carbon dioxide, which then hydrolyzes to ammonium ions and bicarbonate. Binding to available cations then produces carbonate apatite and magnesium ammonium phosphate. Carbonate apatite begins to crystallize at a urine pH greater than or equal to 6.8 while struvite precipitates only at a pH greater than or equal to 7.2 ***(Bichler et al., 2002).***

Citrate normally forms complexes with calcium (Ca2) and magnesium (Mg2), but this protective effect is lost in infective conditions because the high concentrations of bacteria metabolize the citrate **(*Bichler et al., 2002).***

‘‘Struvite–apatite dust’’ is formed around the bacteria and facilitates crystal growth. Crystallization may occur both intra and peribacterially. Apatite crystals grow inside the bacteria and, after bacteriolysis, Microliths formed may serve as a nidus for stone formation. Crystals growing peribacterially may settle on the bacteria and form a phosphate cover,and bacteria enclosed within the stone serve as a source of recurrent infections. Stone propagation occurs extremely quickly because of the constant supply of reactants and the alkaline milieu, in which struvite and apatite are poorly soluble. Additional pathogenic factors include the formation of an exopolysac-charide biofilm (***Choong and Whitfield, 2000).***

Inflammation also leads to increased mucus secretion, which in turn acts as a matrix for crystal aggregation. Finally,

ammonia induces damage to the surrounding protective urothelial glycosaminoglycan layer and thus increases bacterial adherence to the transitional epithelium **(*Rahman et al., 2003)***. Struvite stone formation typically occurs in patients with recurrent urinary tract infection and retained urine. Predisposing factors include urinary tract obstruction, chronic indwelling catheter, urinary diversion, and neurogenic voiding dysfunction ***(Bichler et al., 2002).***

Most women with struvite stones have a normal urinary calcium excretion and likely form pure struvite stones de novo after a urinary tract infection. Pure struvite stones also form in other patients prone to infection, such as those with a ureteral diversion or neurogenic bladder. Meanwhile, mixed stones made up of struvite and calcium carbonate apatite occur in some women and most men. Presumably these hypercalciuric patients begin with calcium-oxalate stone formation and develop superimposed infection with struvite deposition.

2- Pathogenesis of other possible rare composition of staghorn calculi

A- Uric acid stones

The process of uric acid stone formation once uric acid crystals precipitate has not been fully elucidated. Although some investigators have suggested that uric acid crystal adhesion to kidney epithelial cells ***(Koka et al., 2000)*** and

inhibitors such as glycosaminoglycans ***(Ombra et al., 2003)*** may play a role in uric acid stone formation.

The three main determinants of uric acid stone formation are low pH, low urine volume, and hyperuricosuria The most important pathogenic factor is low urine pH, because most patients with uric acid stones have normal uric acid excretion but invariably demonstrate persistent low urine pH ***(Pak et al., 2003a).***

Although the pathogenesis of low urine pH in idiopathic uric acid stone formers is not known with certainty and may be multifactorial, several potential mechanisms have been proposed. ***Sakhaee and colleagues (2002)*** first observed that normouricosuric individuals with pure uric acid stones were more likely to have diabetes mellitus or to demonstrate glucose intolerance than normal individuals or those with mixed uric acid/calcium oxalate or pure calcium oxalate stones. ***Pak and colleagues (2003)*** noted a higher prevalence of uric acid stones and low urinary pH among patients with non—insulin-dependent diabetes (34%) than among nondiabetic stone formers. Furthermore, uric acid stone formers have been found to share many of the characteristic features of the metabolic syndrome (a condition defined as insulin resistance), including hypertriglyceridemia, hyperglycemia, obesity, and hypertension ***(Sakhaee et al., 2002; Pak et al., 2003b).***

Another potential mechanism for uric acid stone formation is loss of diurnal variation in urinary pH. In most individuals there is diurnal variation in both serum and urine pH, with alkalinization of the urine noted in the morning and after meals ***(Niv and Fraser, 2002).*** After consumption of a meal, secretion of gastric acid into the stomach lumen leads to compensatory base excretion by the parietal cells into the serum, resulting in transient alkalinization of the blood and urine, the so-called alkaline tide. ***Murayama and coworkers (2001)*** also found consistently low urinary pH (<6) in uric acid stone formers evaluated on both controlled metabolic and random diets and found absence of the postprandial and morning alkaline tides. In contrast, calcium oxalate stone formers maintained diurnal variation in urinary pH. Transient alkalinization of the urine may be sufficient to protect normal individuals from uric acid stone formation. The underlying cause of the absence of a urinary alkaline tide in uric acid stone formers is unknown but may be due to a renal defect rather than a gastric one ***(Maalouf et al., 2004).***

B- Cystine stones

Cystinuria is an autosomal recessive disorder characterized by a defect in intestinal and renal tubular transport of dibasic amino acids, resulting in excessive urinary excretion of cystine (***Ng and Streem, 1999).*** Although the defect results in high urinary concentrations of lysine, ornithine,

and arginine as well, the poor solubility of cystine leads to stone formation. In children, cystinuria is the cause of up to 10% of all stones ***(Faerber, 2001; Erbagci et al., 2003 and Knoll et al., 2005).***

Under normal conditions amino acids are freely filtered by the glomerulus and almost completely reabsorbed in the proximal tubules. In cystinuria, the defect in transport of cystine results in high urinary levels.

There are several factors that determine the solubility of cystine, including cystine concentration, pH, ionic strength, and urinary macromolecules. The main contributor to cystine crystallization is supersaturation because there is no specific inhibitor of cystine crystallization in the urine ***(Pak and Fuller, 1983).*** Because of the poor solubility of cystine in urine, precipitation of cystine and subsequent stone formation occur at physiologic urine conditions ***(Joly et al., 1999).*** The solubility of cystine is highly pH dependent, with solubilities of 300 mg/L, 400 mg/L, and 1000 mg/L at pH levels of 5, 7, and 9, respectively ***(Dent et al., 1955)***. Ionic strength also influences solubility, and as much as 70 mg of additional cystine can be dissolved in each liter of solution as ionic strength increases from 0.005 to 0.***3 (Pak and Fuller, 1983).*** Macromolecules such as colloid also increase cystine solubility, although the mechanism is unclear ***(Pak and Fuller, 1983).*** Therefore, cystine is more soluble in urine than in synthetic solution

The genetics of cystinuria have been studied extensively. To date, two genes involved in the disease have been identified, *SLC3A1* and *SLC7A9*, which have been found to be associated with defects in heteromeric amino acid transporters (HATs). Historically, three types of cystinuria have been recognized in humans: type I, type II, and type III ***(Rosenberg et al., 1966).*** However, this classification correlates poorly with molecular findings, and therefore it has recently been revised by International Cystinuria Consortium (ICC) to take into account the chromosomal localization of the mutation: type A (chromosome 2), type B (chromosome 19), and type AB (both chromosomes) ***(Dello Strologo et al., 2002).*** Homozygotes with the condition exhibit urinary cystine levels as high as 2000 mol/g of creatinine. Review by the ICC revealed that the average age at first stone diagnosis was 12.2 years, with mean number of stone episodes of 0.42 and 0.21 per year occurring in men and women, respectively ***(Dello Strologo et al., 2002).*** Although mean urinary cystine levels are significantly higher in heterozygotes with type B abnormalities (475 mol/g creatinine) compared with those with type A abnormalities (70 mol/g creatinine), there is no difference in stone formation between the two groups, and, in fact, stone formation is uncommon ***(Dello Strologo et al., 2002).***

C- Calcium oxalate stones

Hypercalciuria

Hypercalciuria is the most common abnormality identified in calcium stone formers ***(Pak et al., 1982; Coe et al., 1992 and Bushinsky, 1998)***.

The normal kidney filters approximately 270 mmol of calcium daily and reabsorbs all but 4 mmol**.** However, a variety of conditions lead to elevated urinary calcium levels and increased urinary saturation of calcium salts. Criteria defining hypercalciuria are variable, but the strictest definition classifies hypercalciuria as greater than 200 mg of urinary calcium/day after adherence to a 400-mg calcium, 100-mg sodium diet for 1 week ***(Menon, 1986). Parks and Coe (1986)*** defined hypercalciuria as excretion of calcium of greater than 4 mg/kg/day or greater than 7 mmol/day (men) or 6 mmol/day (women).

Absorptive Hypercalciuria

Absorptive hypercalciuria (AH) is defined by increased urinary calcium excretion (>0.2 mg/mg creatinine) after an oral calcium load. Although fasting urinary calcium is usually normal in AH (<0.11 mg/dL glomerular filtration), severe forms of AH may occasionally be associated with fasting hypercalciuria as well. The underlying pathophysiologic abnormality in AH is increased intestinal absorption of calcium,

which occurs in approximately 55% of stone formers ***(Menon, 1986).*** AH is classified as type I when urinary calcium remains high despite a low calcium diet (400 mg dietary calcium daily) and type II when urinary calcium normalizes with a restricted calcium intake. The added systemic load of calcium due to intestinal calcium hyperabsorption results in a transient increase in serum calcium, which suppresses serum PTH and results in increased renal filtration of calcium, ultimately leading to hypercalciuria. Because the increase in intestinal absorption of calcium is matched by enhanced renal calcium excretion, serum calcium level remains normal.

The cause of increased intestinal absorption of calcium has been variously ascribed to vitamin D—independent and dependent processes, as well as to upregulation of the vitamin D receptor ***(Breslau et al., 1992).*** However, no proposed mechanism completely accounts for all the findings associated with absorptive hypercalciuria, and there is no clear evidence that upregulation of intestinal calcium absorption is the primary cause. However, hypersensitivity to vitamin D has been shown to increase intestinal calcium absorption ***(Bushinsky, 1998).*** Moreover, several studies have linked hypercalciuria with the vitamin D receptor (VDR) gene. ***Jackman and coworkers (1999)*** identified a polymorphism in the VDR gene in 19 patients with a family history of nephrolithiasis and hypercalciuria, thereby establishing a potential link.

Renal Hypercalciuria

The kidney filters approximately 270 mmol of calcium and must reabsorb more than 98% of it to maintain calcium homeostasis ***(Bushinsky, 1998).*** Approximately 70% of calcium reabsorption occurs in the proximal tubule, with paracellular pathways predominating ***(Frick et al., 2003).*** In renal hypercalciuria, impaired renal tubular reabsorption of calcium results in elevated urinary calcium levels leading to secondary hyperparathyroidism ***(Coe et al., 1973).*** Serum calcium level remains normal because the renal loss of calcium is compensated by enhanced intestinal absorption of calcium and bone resorption as a result of increased secretion of PTH and enhanced synthesis of $1,25(OH)_2D_3$.

High fasting urinary calcium levels (>0.11 mg/dL glomerular filtration) with a normal serum calcium value are characteristic of renal hypercalciuria**.** The elevated fasting urinary calcium and serum PTH levels differentiate renal from absorptive hypercalciuria.

The actual cause of renal calcium leak is not known, although various theories have been proposed involving renal injury, structural abnormalities, and functional defects ***(Sutton et al., 1980; Yendt et al., 1981).*** Excessive dietary sodium intake may lead to changes similar to those seen in patients with renal hypercalciuria ***(Breslau et al., 1982).*** However, Pak found