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Welcome to the Stone Age: minimally invasive treatments for urolithiasis

Weltings, S.

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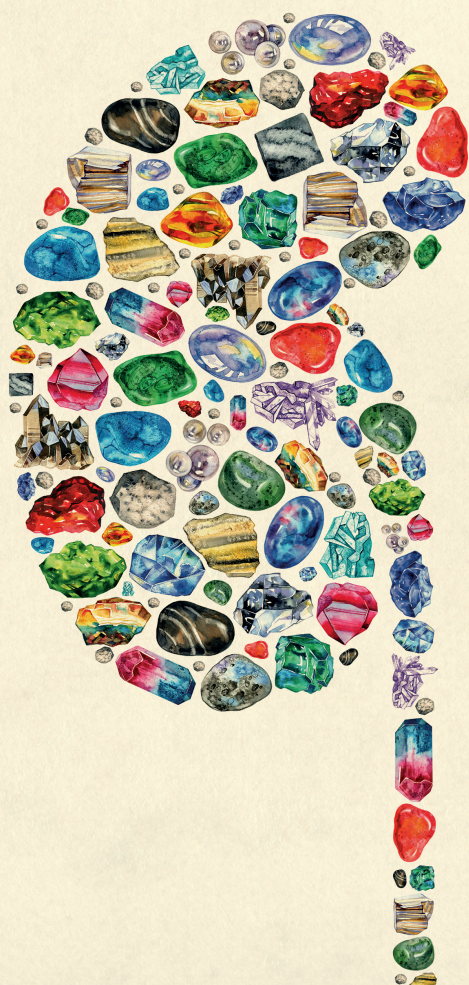
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General introduction and outline of the thesis



INTRODUCTION

This thesis

Kidney stones cause a high burden for health care economy due to their high risk of recurrence and the cost of hospitalization and surgery[1]. Awaiting spontaneous passage of ureteral stones is very often associated with a lot of pain, absence from work and healthcare interference as a consequence. Mortality in urolithiasis however is rare and patient care focuses on treatment of stones rather than prevention.

The main focus of this thesis is on pain management and treatments of urolithiasis. Research on urolithiasis is less common than oncologic subjects in the urologic field, probably for a significant part explained due to a lack of sponsoring. However, the patient with urolithiasis accounts for a large percentage of the urologists' work and complications occur regularly. Many research questions are still unanswered. Some therapeutic regimens have already been used for years, although scientific evidence is missing.

The aim of this thesis is to improve our knowledge, our practice and our standards when treating urolithiasis. The studies in this thesis have taken place in the region of Leiden and The Hague between 2011 and 2020.

History of stone surgery

In the beginning of the 20th Century, the anatomist Elliott Smith, discovered a calculus in the pelvis of a mummy taken from an Egyptian tomb[2]. This stone, dating from 4800 BC had a uric acid nucleus and encrustation of calcium oxalate and ammonium magnesium phosphate. It was probably a bladder stone.

Bladder stones were a common disease in history. Ancient physicians already knew that removing stones required special skills. Hippocrates even warned in his oath: "I will not cut for stone, even for patients in whom the disease is manifest. I will leave this operation to be performed by practitioners, specialists in this art" [3]. The profession of the lithotomist was born.

The first surgical approaches were described in *De Re Medicina*, written in the year 20 Anno Domini (AD) and required 2 main surgical instruments; a knife and a hook[4]. During the described procedure, the bladder was reached through the perineum. The patient was held in the jack knife position that is still used for the transurethral surgical approach. A finger of the left hand was placed in the rectum to push the stone against the perineum and a deep incision from perineum towards the bladder was made. The

stone was pushed out with the finger of the left hand in the rectum. If that was not successful, the hook was used to pull out the stone. Afterwards the wound was dressed with oil and wool. It must have been a very unpleasant procedure, since anesthesia had not been invented.

This procedure was performed for centuries. Many patients suffered incontinence, fistulas, abscesses and 50% of the patients died.

A drawing of a famous episode from 1475, illustrated the vivisection of a man with symptoms of urolithiasis. He was a member of an archers' company in Meudon who had committed a crime and was sentenced to death. The physicians and surgeons of Paris wanted more knowledge of common diseases, including urolithiasis. They sent a petition to Louis XI. The criminal was offered a stay of execution if he agreed to be anatomized alive. The archer survived the procedure.



Earliest operation for the stone, performed in presence of king Louis, by Germain Colot in the cemetery of St Severin, January 1474. Lithograph by A. Rivoulon, 1851.

Other approaches became more common in the 16th century. The first suprapubic cystotomy for the removal of bladder stones was carried out by Franco, a surgeon in Lausanne, France in 1559. He performed the procedure on a child, who survived his surgery[5].

Interventions on kidney stones were only described years later. The first percutaneous nephrostomy was performed in 1865 by dr. Thomas Hillier from Gloucestershire. He repeatedly tapped the hydronephrotic kidney of a four-year-old boy[6]. During this period improvements were made in instrumentation. The first ureteroscopy was performed by Hugh Hampton Young, an American surgeon and urologist, in 1929[7].

The stone

Kidney stones are formed when urine is supersaturated with stone forming salts. At this point, no more of the salt can be dissolved in the urine. This causes molecules to cluster and form a nucleus, the beginning of a crystal. The most common salts are calcium, oxalate, citrate or phosphate.

There are three theories on how the nucleus could originate.

- The first theory is the nucleus forms by clustering on a foundation of interstitial calcium phosphate following loss of urothelial covering of the renal papilla. This foundation is called Randall's plaque.
- The second theory is that small crystals form in the lumen of a nephron at sites of cell injury. When they attach and grow, they form an intraluminal plug. When this reaches the minor calyx, it may be transported with urine or be retained in the kidney.
- The last theory is that free particle formation occurs when the nucleus forms in the renal pelvis by supersaturation of urine[8].

Most nuclei or "mini-stones" are asymptomatic and pass with the urine. Retaining a nucleus or small crystal and exposing it to urine, causes encrustation. An aggregate of these crystals together with an organic matrix (e.g. certain lipids and proteins), form the basis of a kidney stone [9,10]. Supersaturation of urine and crystal formation is influenced by low volume of urine, urinary pH, metabolic diseases, infection and the use of certain medication. Depending on these influencing factors and genetics, other types of stones might form as well. Compositions of phosphate, uric acid, struvite and cystine are seen in daily practice[11]. Knowledge of stone composition may help in analyzing metabolic disorders or prevention. Uric acid stones for instance can be treated by dissolution using alkalinizing of urine. In this case a surgical procedure could be avoided.

Epidemiology

Urolithiasis is highly prevalent and growing in incidence. The increase is related to dietary factors and obesity. However, improvement of detection methods has also resulted in a growing number of patients. The difference in prevalence is determined by various factors. Geography and social health determine fluid intake, climate, diet and occupation. Prevalence among men is higher than it is in women, although the gender gap is narrowing. Also, age influences the likelihood of stone formation, with peaks in the fourth to sixth decades of life.

Prevalence reported in literature is as high as 20% in men in Saudi Arabia and as low as 3% in Icelandic women[12]. The prevalence of urolithiasis in developing countries is probably underestimated. One study reported that urolithiasis was diagnosed with ultrasound in 3% of asymptomatic patients[13].

In children urolithiasis is diagnosed less frequently. Historically, urinary tract anomalies were a major cause for urolithiasis in the pediatric population, but better diagnosis and treatment have decreased this as a factor[14]. An underlying metabolic disorder is the most common cause nowadays, sometimes associated with a urinary tract infection.

Pathophysiology of renal colic

An obstructing ureteral stone is known to cause excruciating pain in waves. We do not fully understand the exact mechanism that causes pain in renal colic. What we do know is that the obstruction of a stone may cause an increased intraluminal pressure in the collecting system. Because of this, the tissue is stretched and the nerve endings in the wall of the system (lamina propria) are stimulated. The smooth muscle in the wall of the ureter will contract as a reaction to move the stone. When the muscles of the ureteric wall are unable to move the stone because it is fixed in one position, they develop a spasm. As a result of spasm, lactic acid is produced which subsequently stimulates the A and C fibers and afferent impulses are sent to the spinal cord. Pain is the result. Local irritation, edema and inflammation are contributing factors for pain as well[10].

We do not fully understand why patients with stones in the urinary tract and hydronephrosis, are sometimes free of pain as well. In some cases, particularly when the stone is at the uretero-vesical junction, urinary symptoms predominate, such as frequency and urgency.

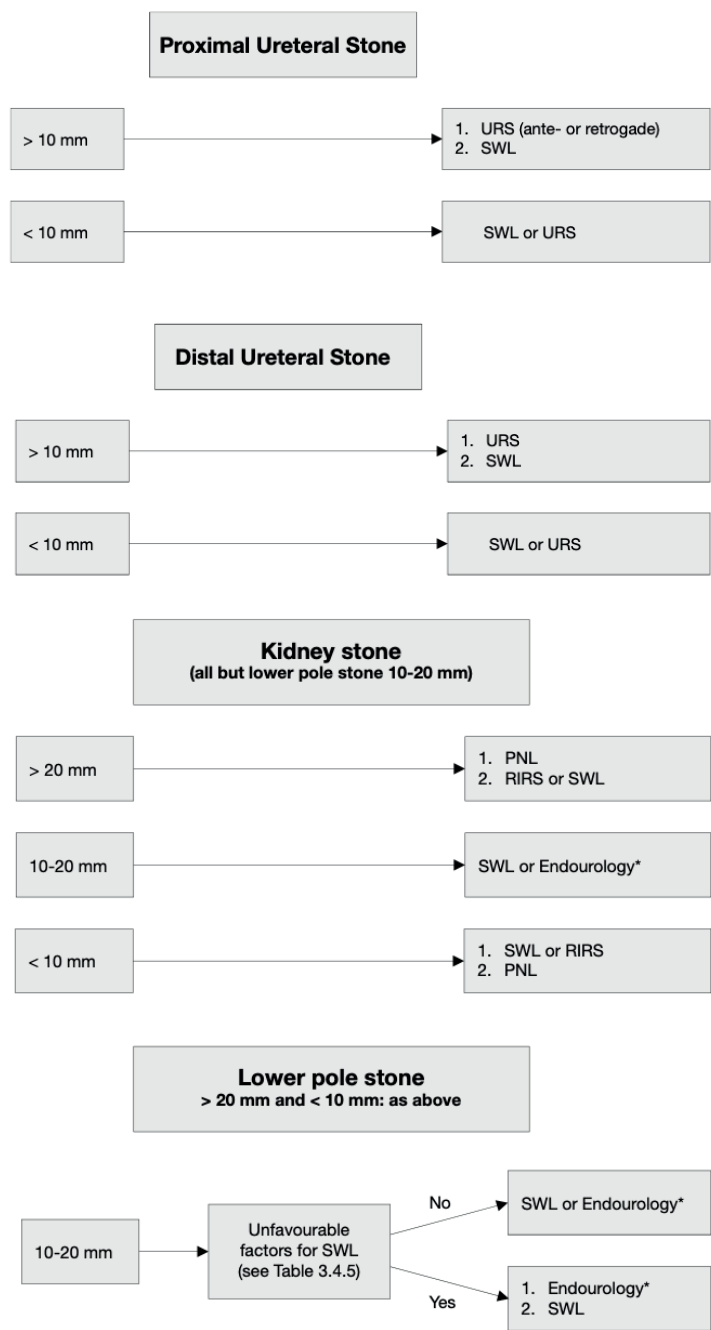


FIGURE 1. Treatment algorithm for ureteral and kidney stones if indicated. Source; EAU guideline urolithiasis 2019

Current practice

Treatment of urolithiasis is mostly started with conservative management using analgesics and supportive management to allow the stone to pass spontaneously. A different approach is used when a stone does not pass spontaneously, or causes pain or when renal function or clinical condition is impaired.

Extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS) and percutaneous nephrolitholapaxy (PCNL) are the main treatment options.

ESWL, the non-surgical option, is only possible if a stone is relatively small, not located near the ureterovesical junction (UVJ) and when visualization using fluoroscopy or contrast is possible.

URS and PCNL are endourological treatment options and could be combined as well.

Which surgical approach is used depends on many factors, such as stone location, stone size, patient anatomy, hospital logistics and patients' preference. The flow chart in figure 1 points out the treatment algorithm.

THESIS OUTLINE

Part 1; Anatomy and diagnostics

Anatomy of the pyelocaliceal system is studied and described in this first part. Knowledge of the renal anatomy is essential for an endourologist. With adequate information on the pyelocaliceal system it is possible to manage expectations regarding stone passage, surgical approach and instruments needed for endourological treatment.

3D reconstructed CT urography was used to compare the different segments in the kidney in **chapter 2A**. A clockwise system was used to describe the measurements. Results should be taken into account when planning an endourological procedure, to improve access and outcome.

In addition to improving outcomes, prevention of stone formation is also gaining attention. Science on stone formation, intrarenal flow and stone passage will help us understand why one patient will be more affected than the other. In **chapter 2B**, another set of 3D reconstructed CT urography images were used to compare stone forming and non-stone forming kidneys.

Part 2; Treatments evaluated

The aim is to assess current endourological treatments to understand where improvement might be necessary. Transparency and accountability of healthcare providers has recently gained interest. When quality and clinical performance are understood in a disciplined way, it could make a substantial contribution to the value of healthcare and its improvement[15].

Chapter 3 describes the quality of stone treatments with URS and PCNL in 2 main hospitals in The Hague. Success rates, complications and outcome are compared with existing literature.

In **chapter 4** we systematically reviewed the optimal drainage method for obstructive urolithiasis. Practice patterns differ globally and choices are due to experience, availability and logistics. With this review we aim to advice on the best treatment option depending on the patient situation.

Part 3; New insights

Pain is the central subject of this last part. In **chapter 5, 6 and 7** current treatments for urolithiasis are critically researched.

The buscopan study, described in **chapter 5**, was designed to close the gap in literature on the use of butylscopolamine in the treatment against pain in patients with renal colic. This antispasmodic drug is still used daily in hospitals in Belgium and in the Netherlands, however scientific evidence is missing. In a double blind and placebo-controlled randomized clinical trial the effect of butylscopolamine on pain was researched.

Pain during treatment with ESWL is evaluated in **chapter 6**. ESWL is a first step in many cases when treatment for urolithiasis is necessary. The hypothesis is that higher pain scores might impair outcome of ESWL. We investigated the influence of pain and patient comfort on the outcome of ESWL.

Chapter 7 examines indications, success rates and complications of antegrade ureteral stent placement. When drainage of the urinary tract with a ureteral stent is indicated, most of the time the retrograde route is used. In this chapter a retrospective data analysis is performed of the antegrade approach in a large hospital in The Hague.

Part 4; Conclusion

In **chapter 8** this thesis is discussed with a view on future perspectives.

Finally, **chapter 9** summarizes the findings from chapters 2 – 7.

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