Analysis of the movements of kidney stones

Analysis of the movements of kidney stones with the help of 4D ultrasound. A cooperation project between the institute of technical cybernetics at NTNU, clinic of image diagnostics and urologic department at St. Olav’s hospital.

Written by Oda Kragset
i Acknowledgements

Thanks to;
Carl-Jørgen Arum for useful guidance and editing, and his motivating enthusiasm.

Thomas Finsen for teaching me how to do clinical examinations of kidney stones with ultrasound.

Ingrid Høye, Harriet Birke and the staff at the daysurgery centre at St. Olav’s hospital for helping me contact the patients and cooperation during examinations.

Asbjørn Støylen and Alfonso Rodriguez-Molares for teaching me how to use an ultrasound machine and for helping me with problem solving along the way.

Sébastien Muller for guidance and help with analysing the ultrasound recordings.

Geir Mathisen, Thomas Langø, Janne Beate Lervik Bakeng and Daniel Høyer Iversen at SINTEF for contributing.

Anne and Asle Kragset, my parents, for reading through my assignment and supporting me.
Objective
The main purpose of this pilot study was to gather information on the movements of kidney stones in a 4 dimensional (4D) perspective through a respiratory cycle, making time the first dimension and space the three remaining dimensions. This information was gathered with 3D ultrasound. To date researchers have published studies utilizing 2D ultrasound to track kidney stones. Still, to this date there are very few research papers where 3D ultrasound has been used for the same purpose.

Additional objectives of this study were to explore the possibilities for digitalizing the data from the 3D ultrasound followed by analysis of the data in navigation software currently available at our institution. Individual patient variables were recorded. The final objective was a detailed analysis of 4D kidney stone trajectory.

Materials and methods
The kidney stones of 20 patients were examined with 3D ultrasound in connection with planned extracorporal shockwave lithotripsy (ESWL) treatment at St. Olav’s hospital day surgery unit between August and October 2015. Written consent was obtained from all 20 patients, and the study was approved by REK. Ultrasound data of 20 patients were obtained, 5 patients were excluded due to no kidney stones found at the ultrasound examination. In November 2015 supplemental clinical information was gathered from the 15 remaining patient journals. Due to analytical difficulties only 5 of the ultrasound recordings were available for the final analysis. All recordings were analysed in cooperation with Sébastien Muller at SINTEF.

Results
The 3D ultrasound data was successfully digitalized and stone trajectory was reconstructed in navigation software. Results were presented in 2D graphs showing the stones’ displacement in three perpendicular directions, and 3D graphs showing a reconstruction of the kidney stones’ trajectory from the analysis results. In all patients the 3D analysis revealed that stone movement was confined primarily to one plane. Range of movement was approximately 5-15 millimetres. Analysis of stone movement during respiratory cycles revealed that the time period of least movement was at the completion of exhalation. Comparing the graphs to the respiratory curves, the stones barely moved at the end of compared to the start of the respiratory cycles. The stones seem to follow a regular rather than a random path of motion. Both reviewing the ultrasound recordings and studying the similarities between 2D graphs suggest certain patterns of movement. Pearson’s and Spearman’s method also show statistically significant correlation between the kidney stone’s movement during 1. and 2. respiratory cycles in most patients. Cross-correlation analysis could not be performed in 10 patients because the ultrasound recordings had a too narrow sector was used. Recordings containing more respiratory cycles would have been beneficial in establishing better reproducibility.
Conclusion
The results address several aspects of ESWL-treatment. The movement analysis reveals that stones have little or no movement at the end of exhalation, suggesting that the optimal time to activate the ESWL energy would be at the end of exhalation. Results also suggest that 2D ultrasound will often be sufficient for tracking of kidney stones; however, 3D ultrasound should be considered as some stones might have 3D movements. This pilot project has revealed several details in the settings used for the actual probe that will better enable the navigation software to accurately follow stone movement. Real-time 3D ultrasound stone tracking combined with navigation analysis on stone-trajectories might potentially lead to greater treatment efficiency in ESWL-treatment.
iii Contents

i Acknowledgements 2

ii Summary 3

iii Contents 5

1. Introduction 6
   1.1 Aim of the study 6

2. Background 7
   2.1 Epidemiology 7
   2.2 Risk factors 7
   2.3 Diagnosis 8
       Symptoms 8
       Diagnostic imaging 8
       Metabolic work-up 9
   2.4 Treatment 10
       Pretreatment 10
       Non-invasive treatment 10
       Invasive treatment 12
       Treatment options 17
   2.5 Prevention 18

3. Literature review 19

4. Material and methods 22
   4.1 Study design 22
       3D ultrasound 22
       Programs 22
   4.2 Study population 23
   4.3 Data gathering 24
       4D ultrasound recordings 24
       Data from patient journals 24
       Confidentiality 24
   4.4 Analysis 25
       Space and time resolution 25

5. Results 27
   5.1 Presenting the results 27
   5.2 Limitations to the analysis method and solutions to these 31
   5.3 Statistical analysis of the results 32

6. Discussion 35
   6.1 Interpretation of the results 35
   6.2 ESWL-treatment today 37

7. Conclusion 39

8. Bibliography 41

9. Appendices 48
   Appendix A. 2D-, 3D- and correlation graphs 48
   Appendix B. Research information and compliance form – 01.12.14 60
   Appendix C. Omitted sections 65
   Appendix D. MATLAB autocorrelation code 71
1. Introduction

Kidney stone disease (nephrolithiasis) is a common problem amongst the western population. Most kidney stones are small and pass spontaneously. These patients often need no further treatment. However, some nephrolithiasis patients develop large stones, which can cause significant morbidity in the form of acute symptoms and chronic complications if they are not treated. Yet effective treatment and prevention may eradicate the disease completely.

ESWL is the first choice of treatment for nephrolithiasis. Unfortunately, there are limitations to the treatment. Due to breathing and other movements only about 50% of the shock waves actually hit the stone. The remaining shock waves hit surrounding tissue, which can potentially cause pain and complications. By analysing the kidney stones’ 3 dimensional (3D) movements, over a short period of time and in different subjects, we wish to better understand this movement and potentially be able to predict the stones’ future position. This prediction could be used to adjust the timing and focal point of the ESWL machine’s shock wave generator so that more of the shock waves hit the stone and thereby increase treatment efficacy.

Currently, fluoroscopic x-ray and ultrasound are used for visualization of the stone during treatment. Both these tools are limited, as they only produce 2 dimensional (2D) images of the stone, and as the stone probably moves in 3D these 2D imaging modalities could be insufficient. At our institution fluoroscopic imaging has been the mainstay of ESWL stone localization and thereby exposing the patient and hospital staff to radiation.

1.1 Aim of the study

The main purpose of this pilot study is to gather information on the movements of kidney stones in a 4 dimensional (4D) perspective through a respiratory cycle, making time the first dimension and space the three remaining dimensions. This information will be gathered with 3D ultrasound. So far researchers have published many studies utilizing 2D ultrasound to track kidney stones (chapter 3). Still, to this date there are very few research papers where 3D ultrasound is utilized for the same purpose.

The second objective is to, explore the possibility of digitalizing the ultrasound images in such a manner that the data can be simultaneously analysed in a navigation program.

The trajectories of the stones will then be compared to;

- Main variables: The patient’s respiration movements and –frequency;
- Inter-individual variables: Sex, age, body mass index (BMI), weight, height, and if present kidney anomalies or lung conditions affecting the stones’ movements;
- Kidney stone variables: The stone’s placement in the kidney (right versus left kidney, upper versus central versus lower pole, anterior versus posterior), size, density and number.

An evaluation of the stone’s movements will also be conducted to consider whether the stone follows a regular rather than a random path of motion. If this is the case the stone’s future position might be predictable.
All data gathered through this study, especially the question regarding the stone’s path of motion, will be of help to the doctorate Robot-Assisted tracking of kidney Stones using Medical UltraSound (RASMUS). This project wishes to develop a robot arm capable of accurate, real-time tracking of kidney stones with ultrasound, which ultimately will lead to more effective ESWL-treatment.

Objectives in the RASMUS study are;
- Increase the quantity of shock waves striking the kidney stone, and lower the amount of shock waves to surrounding tissue;
- Reduce the patients’ pain and thereby reduce the need of anaesthetic personnel;
- Make the treatment safer and reduce bleeding complications and admissions;
- Lower the need of fluoroscopic x-ray use to spare patient and health care personnel of unnecessary radiation;
- Lower the need of re-admissions;
- Make the treatment more efficient so that more patients are treated per day, and the waiting lists are reduced.

2. Background

2.1 Epidemiology

Kidney stone disease (nephrolithiasis) is a common disease that through the last decades has become even more common. The changes in American epidemiology were examined in a nationwide study based on National Health and Nutrition Examination Survey II (NHANES II) and NHANES 2007-2010. The results showed a marked increase in prevalence, as the disease had gone up from 3,2% in the period 1976-1980 to 8,8% in the period 2007-2010 (1, 2). Europe seems to be following the same trend. An Italian study of the population in Rome showed increasing prevalence from 11,7 to 17,2 out of 1000 inhabitants in the period 1983 to 1993-1994 (3). The increase is mainly attributed to women. 40 years ago 3 times more men than women were diagnosed with nephrolithiasis in the United States. Recently this has changed as the incidence in men has dropped, except for the 70 years plus group, while the incidence in women has risen. Now the men-women ratio is 1,3, meaning men only have a slightly higher risk of nephrolithiasis compared to women (4).

2.2 Risk factors

Lately several studies have been conducted to identify risk factors of nephrolithiasis. Many have concluded that obesity is a major risk factor of nephrolithiasis (5-8), where obese patients are defined as having a Body Mass Index (BMI) of 30 kg/m² or more (9). The wave of obesity in developed countries may in fact be one of the main reasons for the rising incidence of kidney stone disease. This is what Taylor et al. found as they analysed three large cohort studies (6), the Health Professional Follow-up Study (HPFS), the Nurses’ Health Study I (NHS I) and the Nurses’ Health Study II (NHS II).

Fluid intake has been inversely correlated to risk of nephrolithiasis (10-12). As a consequence, EAU guidelines recommend that nephrolithiasis patients drink at least 2,5 litres of fluid every 24 hours to eliminate this risk factor (13). Patients are also advised to reduce calcium intake, but only supplementary calcium, as studies have shown that
dietary calcium reduces the nephrolithiasis risk (11, 14). Another dietary risk factor is sodium chloride, which should also be restricted in nephrolithiasis patients (15, 16).

In several studies kidney stone formation is significantly increased amongst people with a positive family history compared to people with no such history. The HPFS examined a population of 37,999 male participants in 1986, concluding that the relative risk of developing the disease in patients with family history of nephrolithiasis was estimated to 2.57 (95% CI, 2.19 to 3.02) (17).

2.3 Diagnosis

Symptoms
Kidney stones may be asymptomatic or symptomatic. Asymptomatic stones are typically found in patients having radiological imaging of the abdomen, and most of these stones stay asymptomatic (18). Symptomatic stones usually stem from the passage of stones from the kidney into the narrower ureter, leading to obstruction of the urinary collective system and subsequent hydronephrosis. Distension of the renal capsule cause flank pain known as renal colic. The pain often fluctuates because of spasms in the ureter, it usually lasts for 20-60 minutes, and it might range in intensity from almost unnoticeable to severe pain. Flank pain together with gross or microscopic hematuria and a positive KUB x-ray is the best predictor of nephrolithiasis (19). However, absence of hematuria does not exclude the diagnosis (20, 21). Other symptoms are nausea, vomiting, dysuria and urgency.

Diagnostic imaging
Which diagnostic imaging one should choose depends upon the patient’s symptoms and medical history, and so a detailed anamnesis should be done beforehand. Imaging should not delay administration of pain relief and other emergency measures the patient might be in need of. An exception is if one is uncertain of the diagnosis and the patient has either fever or a solitary kidney as these situations indicate serious illness.

Ultrasound (US)
Ultrasound is considered the primary diagnostic tool in patients with nephrolithiasis. There are many reasons for this. Ultrasound is considered safe, as it is non-invasive and does not involve any radiation. It is also a fast, inexpensive and reproducible method of imaging. As for application ultrasound can detect both radiolucent and radiopaque stones. It can locate stones in the kidney’s calices and pelvis and in the pyeloureteric- and vesicoureteric junctions. If the stones are located in the ureter, where ultrasound cannot be used to display it, ultrasound can still visualize a subsequent upper urinary tract dilatation. The main downside considering ultrasound is that it is an operator dependent method, which might cause a low sensitivity. A review comparing several other studies showed that sensitivity varied between 19-93% while specificity was relatively high at 82-100% (22).

Kidney-Ureter-Bladder radiography (KUB radiography)
KUB radiography is a plain x-ray of the abdomen, including the kidney, ureters and bladder. The advantage compared to ultrasound is the ability to differentiate between radiopaque and radiolucent stones. Still it is not the preferred choice of imaging because its sensitivity and specificity is low (23-26). KUB radiography can be used in follow-up
of patients, but only if a non-contrast computer topography (NCCT) is not indicated as it does not produce any additional information.

**Non-Contrast Computer Topography (NCCT)**

NCCT is the first choice of imaging in patients presenting with acute flank pain. It recently replaced the previous gold standard intravenous urography (IVU). NCCT has a sensitivity and specificity close to 100%, and thereby outclass the IVU imaging technique considering finding and identifying kidney stones (26-31). There is one disadvantage to not using contrast; one loses information regarding renal function and the urinary collection systems anatomy. An enhanced CT or an IVU should be used if anatomy needs to be assessed before a planned stone removal.

In non-obese patients with stones larger than 3 mm it is recommended to do a low-dose CT instead of a regular-dose CT to protect the patient from unnecessary radiation (32). In Norway a special variation of the CT is in use called the “stein CT”, directly translating to “stone CT”. It differs from a plain helical CT in three ways. Firstly, it does not use contrast, as that would hide the stone. Secondly, it uses low-dose radiation as the stone is solid compared to surrounding tissue and will be visible regardless of the radiation dose. Thirdly, the patient is put in a prone position to differentiate between stones that are stuck in the vesicoureteric junction and stones that have passed on to the bladder.

NCCT, unlike the KUB radiography, can detect both radiolucent and radiopaque stones. There are only a few rare kidney stones consisting of drug residues that are not visible on an NCCT, for example indinavir stones (33). By NCCT one can determine the stone’s diameter, density, inner structure, location and skin-to-stone distance. These factors affect the success rate of extracorporeal shock wave lithotripsy (ESWL) (34-36).

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>Radiation (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUB radiography</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>IVU</td>
<td>1.3 – 3.5</td>
</tr>
<tr>
<td>Regular-dose NCCT</td>
<td>4.5 – 5.0</td>
</tr>
<tr>
<td>Low-dose NCCT</td>
<td>0.97 – 1.9</td>
</tr>
<tr>
<td>Enhanced CT</td>
<td>25 – 35</td>
</tr>
</tbody>
</table>

**Table 2.1. Table showing radiation dosages.**

*From Guidelines on Urolithiasis (13)*

**Metabolic work-up**

Diagnostic imaging can determine whether there is a stone or not, but it reveals little about how the stone came to be. Usually the best way to study the cause of the disease is to analyse stone composition. All recurrent stone patients are asked to filter their urine to retrieve one or more kidney stones. The stones are analysed with infrared spectroscopy or x-ray diffraction. Newly formed kidney stones in recurrent stone formers should be reanalysed if recurrence occurs during pharmacological treatment, if the recurrence happens shortly after complete stone clearance, or if the recurrence
happens after a prolonged time so that the stone composition might have changed (37, 38).

In the work-up for first-time formers the patients get blood- and urine tests. A full blood count and levels of creatinine, uric acid and ionized calcium are measured in blood. If an intervention is likely or planned sodium, potassium, CRP and coagulation tests might also be performed. The urine’s pH, nitrite, and red and white cells are measured, and a microscopy and culture is done. Patients with high risk of recurrence go through a more detailed metabolic work-up (13).

2.4 Treatment

Pretreatment

Analgesia
All nephrolithiasis patients experiencing renal colic should be given medication to obtain analgesia until the stone has passed or has been removed. Non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred pharmacological group, as they work by reducing inflammation locally, and so eliminate the cause of the pain. This way they give better pain relief and reduce recurrence of renal colic compared to the second best pharmacological group, the opioids (39-41). Opioids are also known to induce vomiting, especially Pethidine which because of this should not be used in renal colic patients.

Infections
Urinary tract infections should always be checked for and treated before active stone removal. Urine drainage by stenting or a nephrostomy should also be performed some days prior to treatment (13).

Bleeding diathesis
Such patients should be evaluated to decide whether they can go through treatment if antithrombotic treatment is discontinued or if the treatment is too risky nonetheless. Patients receiving ESWL, percutaneous nephrolithotripsy (PCNL), percutaneous nephrostomy, laparoscopic- or open surgery is at higher risk of developing haemorrhage or perinephritic hematoma. If antithrombotic treatment cannot be discontinued ureterorenoscopy (URS) might be the safer alternative due to less morbidity (42-44).

Non-invasive treatment
95% of kidney stones under or equal to 4 mm in diameter pass spontaneously within 40 days, or often less (45). These patients seldom require any non-invasive or invasive treatment to accelerate stone passing. However, if the stone does not pass on its own, an intervention is recommended as it might cause complications. Stones may grow larger by time, and become more difficult to extract. Depending on the size and location of the stone it might block the urinary collective system, leading to complications as acute and chronic pain, hydronephrosis and possibly infection. To prevent this, a stent or a percutaneous nephrostomy can be utilized as to drain the urine, and non-invasive or invasive methods of stone removal can be initiated.

Medical expulsive therapy (MET)
The therapeutic effect of these drugs is to relax smooth muscle in the ureters. There are two options; tamsulosin, which is a α-1 receptor blocker, and nifedipine, which is a
calcium channel blocker (46, 47). Both work well, but in distal ureter stones Tamsulosin has the best therapeutic effect (48-50). This treatment is contraindicated in some patients. The stone must be expected to pass spontaneously, meaning it has to be less than 5 mm in diameter and located to distal ureter, or it has to be treated with ESWL or ureteroscopy before MET is tried (46, 51, 52). The patient must have little or no pain, enough renal function reserve, and he or she cannot have any clinical signs of infection. This treatment also requires close follow-up at least every 14 days, where the physician checks the stone’s position and a possible hydronephrosis development (13). For the time being this treatment is not used in children as there is too little research on the specific population.

Chemolytic dissolution of stones
Oral chemolytic dissolution of stones is only applied to uric acid stones. The patient is given alkaline citrate or sodium bicarbonate medication orally, which alkalises the urine. At a pH of 6,5-7,2 the stone dissolves (53, 54). This treatment requires good compliance from the patient. He or she must monitor the urine’s pH several times daily with a urine dipstick, and use the urine-pH to modify the dosage of the alkalisering medication.

Percutaneous chemolytic dissolution of kidney stones is done by administrating medication directly to the stone by a nephrostomy catheter. The method works best on infection- and uric acid calculi. The success rate rises if the method is combined with ESWL, as fragmenting the stone increases the surface-area exposed to the dissolving substances. Percutaneous chemolytic dissolution of stones is rarely used because the treatment is complicated and has possible side effects.

Extracorporeal shock wave lithotripsy (ESWL)
Requirements for ESWL-treatment are (13):
- The stone has to be located in the kidney, have a diameter of 4,0-20,0 mm and the appropriate hardness;
- The patient must tolerate the treatment;
- The patient must have normal kidneys.

Patients who are unfit for ESWL are:
- Patients with unavailable stones, meaning the stones are close to bone-structures or the patient is overweight (55-58);
- Patients with uncontrolled urinary tract infections;
- Patients vulnerable for the particular treatment, for example pregnant women and abdominal aortic aneurism-patients (59, 60);
- Patients who bleed easily due to medication or disease. However, if specific treatment is administered to reverse medication ESWL is perfectly safe (61).

In ESWL-treatment high-intensity acoustic pulses emitted by a lithotriptor are used to break the kidney stone. The pulses are focused on the kidney stone by an acoustic lens, and transferred to the patient’s body through a water-filled, cushioned coupling device that is placed directly over the kidney. To optimize the transition of pulses ultrasound gel is used between the coupling device and the skin. Fluoroscopic x-ray or ultrasound is used to track stone movements, aim at the stone and to check whether it has been crushed or not (figure 2.2) (62).
At the start of the treatment the pulses are set to a lower power level to accustom the patient to the treatment, and because this method induces vasoconstriction which reduces renal injury (64-66). It is important that the patient lie still, so most often he or she is sedated or anesthetized. When the patient is prepared the power level is slowly increased to crush the stone. The maximum power level depends on the patient’s pain threshold and the stone’s density. The treatment session lasts for about 30-60 minutes.

The recommended frequency is 1,0-1,5 Hz as higher frequencies are associated with more tissue damage (67). The pulses break up the stone directly by creating shearing forces and indirectly by producing cavitation bubbles. Later the fragments are excreted with the urine, and so it is important that the patient drink sufficiently. Sometimes it may be beneficial to insert a JJ-stent to secure the flow of urine and relax the ureters to accelerate the passing of the stone.

ESWL is considered to be the safest alternative of stone removal. During treatment the patient is exposed to radiation if fluoroscopic x-ray is used as the imaging modality. The radiation-dose depends on the session length necessary to crush the stone, but is often very low (62). The risk of developing complications is low, and most can be prevented or treated easily. The most common complication is regrowth of residual fragments, and can occur in 20% of patients (68, 69). Other fairly common complications are steinstrasse development, renal colic, hematoma development, bacteriuria, sepsis and cardiovascular dysrhythmia (68, 70-72).

**Invasive treatment**

*Percutaneous nephrolithotomy (PCNL)*

This treatment is ideal for patients with staghorn calculi, where the calculus is equal to or more than 20 mm in size and is located to the renal pelvis. The technique described
below is the antegrade approach. There is also a retrograde approach where a thin wire is guided from inside the kidney to the flank skin using a flexible ureterorenoscope.

There are many absolute and relative contraindications for this treatment:

- All contraindications for general anaesthesia apply;
- Patients who bleed easily due to anticoagulation therapy or a disease;
- Untreated urinary tract infection;
- Atypical bowel interposition;
- Tumour blocking the access tract area;
- Malignant kidney tumour;
- Pregnancy.

To secure direct access to the kidney and to make sure none of the above contraindications are present the procedure is guided by imaging such as ultrasound or fluoroscopic x-ray, the latter is associated with more haemorrhaging (73).

The procedure is minimally invasive and requires general- or spinal anaesthesia. A small incision is made on the patient's back directly above the kidney, and a percutaneous nephrolithotomy needle is inserted into the renal pelvis. A guide wire is thread through the needle into the renal pelvis. The needle is then withdrawn leaving the guide wire in place, so that dilators can be passed over it. Standard access tracts are 24-30 French. Smaller ones are also available, and have been shown to reduce bleeding and need of blood transfusions (74, 75). At this stage there is an open channel from the flank skin into the kidney wherein a rigid or flexible nephroscope can be introduced. If the stone is too large it has to be crushed with ultrasonic, ballistic or Holmium:YAG laser devices before taken out. Operators using rigid scopes can use any of the devices, but if using a flexible scope only Holmium:YAG laser is recommended for stone crushing (13). Forceps and nitinol- or steel wire baskets are used to remove the stones (figure 2.3).
Sometimes it is beneficial not to close the access tract to the kidney after surgery. A nephrostomy tube can keep the tract open so that the patient does not have to go through another surgery. Relevant cases are:

- Postoperative residual stones;
- Significant blood loss or bleeding diathesis;
- Urine extravasation;
- Ureteral obstruction;
- Infection stones with persistent bacteriuria;
- Solitary kidney;
- Other planned or possible procedures requiring percutaneous access to the kidney.

Common postoperative complications are fever, bleeding, urinary leakage and problems connected to residual stones. A study reported that 79.5% of patients had an uncomplicated postoperative course (76).

**Ureterorenoscopy (URS)**

This treatment is suited for almost all patients with stones in the renal pelvis or proximal ureter. Some exceptions are patients with anatomical abnormalities, for example ureteral strictures, patients who cannot undergo general anaesthesia, or patients with untreated urinary tract infections. Patients treated with anticoagulants should if possible discontinue these before the intervention, but only have minor increase in complications if they cannot do so (77).
Before treatment starts patient history, physical examination and imaging should be done. The patient should also receive short-term antibiotic prophylaxis (78). Analgesia is achieved by general anaesthesia, or sometimes local- or spinal anaesthesia. Flexible or rigid ureterorenoscopes are used to gain retrograde access to the renal pelvis through the urethra, bladder and ureter. Fluoroscopic x-ray is used to visualize the stone during treatment. Endoscopic forceps or nitinol baskets are used to retrieve the stone. Large stones must be crushed before extraction. The preferred method of intracorporeal lithotripsy is the Holmium:YAG laser, but other devices using pneumatic or ultrasound systems may also be used (figure 2.4) (79).

![Small stone in kidney](image)

**Figure 2.4.** *Figure showing URS-treatment.*
*From University College London Hospitals (63)*

Inserting a JJ-stent is no longer a required part of the URS. However, pre-stenting might be utilized as they facilitate management, improve stone-free-rate and reduce complications (80). Post-stenting should only be utilized in patients with increased risk of complications, because stenting after uncomplicated URS does not improve outcome, but on the contrary contributes to increased morbidity (81). A JJ-stent must be followed up routinely by plain abdominal film (KUB), CT or ultrasound, and should be removed after 1-2 weeks.

Different equipment may be used before or during the procedure to help the surgeon. A safety wire may be used to prevent tools such as JJ-stents from exciting possible perforation-holes in the ureter made during the intervention. Balloon and plastic
dilators may be used to ease insertion of endoscopes. Ureteral access sheaths are recommended as they provide a better view through the endoscope by continuously draining the kidney of urine and preventing the build-up of intrarenal pressure (82).

The complications and complication rates following URS can be seen below (table 2.2). The most dreaded complications are ureteral avulsions and stricures, but these and other complications are infrequent with the current equipment and expertise.

<table>
<thead>
<tr>
<th>Intraoperative complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal injury</td>
<td>2.5</td>
</tr>
<tr>
<td>Ureteral perforation</td>
<td>0.7</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>0.1</td>
</tr>
<tr>
<td>Ureteral avulsion</td>
<td>0.1</td>
</tr>
<tr>
<td>Extraureteral stone</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever or urosepsis</td>
<td>1.1</td>
</tr>
<tr>
<td>Persistent haematuria</td>
<td>2.0</td>
</tr>
<tr>
<td>Renal colic</td>
<td>2.2</td>
</tr>
<tr>
<td>Migrated double-J stent</td>
<td>0.7</td>
</tr>
<tr>
<td>Transitory vesicoureteral reflux (especially in patients with indwelling double-J stent)</td>
<td>4.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureteral stricture</td>
<td>0.1</td>
</tr>
<tr>
<td>Persistent vesicoureteral reflux</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Table 2.2. Complications in connection to URS-treatment.
From Geavlete, et al. (83)*
**Open surgery**

Open surgery is rarely needed nowadays because of other safer treatment options, and is only used in about a couple out of 100 patients (84-86). Nevertheless, it is important in management of complicated cases. Open surgery is indicated if:

- Patient has a complex stone burden;
- Patient experienced failure of ESWL, PCNL or URS procedures;
- Intrarenal anatomical abnormalities or skeletal deformities that prevents or complicates other treatment modalities subsists;
- Patient is morbid obese;
- Patient has comorbidity;
- Patients who needs concomitant open surgery;
- Reduced renal function due to partial or full nephrectomy subsists;
- Patient requests it after failed minimally invasive procedure;
- Stone lies in ectopic kidney which cannot be accessed with ESWL or PCNL;
- Patient has upper ureteral stones.

**Laparoscopic surgery**

Laparoscopic surgery is increasingly replacing open surgery, and can be used in most cases where open surgery is indicated (87, 88). The stone-free-rate is close to 100% if surgeons with expertise are available (89). Though it is effective compared to ESWL and URS, laparoscopic surgery also significantly increases risk of complications (89, 90).

**Treatment options**

Active stone removal is therapies that crush the stone and or remove it directly, such as ESWL, PCNL, URS, laparoscopic- and open surgery. There are some absolute indications for active stone removal. First, if a large or growing stone is not expected to pass spontaneously it has to be removed. Second, a patient with unmanageable symptoms should be treated actively. Third, if kidney function is endangered because of obstruction or infection an intervention should be done immediately. An obstruction of the urinary collective system will cause damage, as the fluid pressure builds up and harms the kidneys functional tissue. If this happens in a patient with a single kidney or there is a patient with bilateral obstructions of the ureters the patient might lose all kidney function. An infection can damage the kidney in a similar way if pyonephrosis develops. An even more dangerous situation is development of urosepsis, which puts all the patient’s organs at risk (91).

Currently the choice of treatment modality is mostly based on the kidney stones size, location and density (92). Other factors that might affect treatment utilized are obesity, bleeding diathesis, composition of the stone or steinstrasse development (13).
2.5 Prevention

General prevention

There are recommendations that all nephrolithiasis patients should follow to prevent recurrence of the disease. These mostly counteract the modifiable risk factors. Fluid intake should be at least 2.5-3.0 litres per day, more in warm environments, to increase urinary output. The diet should contain little sodium chloride and animal protein, should have normal amounts of calcium, and should be rich in vegetables and fibre. The patient should aim at a BMI between 18-25 kg/m² meaning obese patients should reduce bodyweight through daily physical activity and diet adjustments (13).
Specific prevention
Nephrolithiasis patients with high risk of recurrence should receive pharmalogical treatment to prevent stone formation. The stone composition decides what drug and dosage the patient should get (13).

3. Literature review
A PubMed search was preformed to uncover prior knowledge on the subject. The search phrase used: ((kidney stone) OR nephrolithiasis) AND ultrasound[Title] NOT (percutaneous nephrolithotomy). 6 relevant studies were found.

Ever since early 1990 researchers and physicians began thinking that ultrasound monitoring should be preferred in place of fluoroscopy in ESWL-treatment because of all the benefits attached to this imaging-method (93). In 2001 Chang et al. developed and tested ultrasound-based computer software capable of real-time stone tracking (94). The software consisted of these components;

- Stone detection. Certain intensities in a grey-scaled image were selected. Kidney stones appear as bright white on ultrasound images, and so all objects with this intensity would be selected.
- Frame matching. One frame in a recording was compared to the next one, finding the best possible overlap between the two frames. By identifying the stone in the first frame the stone could be found in the next frame. This image recognition was especially useful if the stone slipped in and out of the plane or changed size or shape because of movement, as it then could be difficult to identify it.
- Stone trajectory recording. A program processing images capable of recognizing changes in stone location, and thereby registering the trajectory of the stone.
- Real-time stone tracking. A system able to measure the distance the stone moved from one frame to the next, and use the information to move the shock wave generator in real-time.

An experimental setup was used to test the software together with a LiteMed 9200 lithotripter (figure 3.1). Their study concluded that real-time tracking with ultrasound is possible, and compared to no tracking is both a lot more accurate and effective, meaning respectively less shock waves and time is needed to break the stone. However, a limitation to this system was that it did not function when the stone slipped out of the ultrasound plane.
In 2002 Chang et al. completed another experimental study utilizing the ultrasound-based real-time tracking system. This was an animal study attempting to break an artificial stone inside a pig’s kidney in a Litemed 9200 electrohydralic lithotripter. This time they discovered that tracking led to more of the stone being crushed into tiny pieces or powder.

In 2006 Manousakas et al. used the same lithotripter but with modified software to overcome challenges that arose. The stone detection software could not differentiate between kidney stones and other small, bright artefacts in the ultrasound images. Instead of using a global threshold, where any pixel with a certain brightness was interpreted as a stone, they made use of brightness peek detection. This technique consists of considering neighbouring, bright pixels as one large area, and then discarding all areas which are too small. Another advantage of this method is that even stones that are less bright will be detected.

The second problem Manousakas et al. encountered was separating stones from calcifications in the kidney, as both appear as bright and large areas. By adding recognition of the stone’s acoustic shadow into the stone detection algorithm the team solved this problem. The shadow beneath the stone is an artefact, and it is created when ultrasound waves are incapable of passing through the stone. However, the shadows intensity varies, and will be hard to detect for example when the stone has been fragmented. The same technique described in the paragraph above gave success. Dark areas situated beneath the stone would be compared to the areas left and right of it, and with a sufficient ratio be defined as a stone shadow.

After probable stones have been detected in one frame the program analyses the next frames the same way. If the same probable stone keeps turning up in every frame the
system decides that this is in fact a real stone. All these improvements made this software the most accurate and effective for tracking and treating kidney stones. This was confirmed in 2013 by another study from Chang et al. (97). Still, the limitation experienced by Chang et al. remains; if the stone moves out of the ultrasound plane one can no longer track it.

Abid et al. did a study in 2013 comparing conventional tracking and a stereotaxic navigational system utilizing 3D ultrasound (Visio-Track®) (98). The study achieved its goal by proving that absorbed radiation dosage and treatment time during ESWL was reduced in the 20 patients treated by the system based purely on 3D ultrasound. Another new study, released in 2015 by Abid et al., showed the same results as the Sonolith® i-sys lithotripter with combined fluoroscopy and ultrasound tracking systems was compared to Visio-Track® purely based on 3D ultrasound tracking (99). These two studies did not experience the problem earlier studies had encountered due to the ability to track the stone in 3D.
4. Material and methods

4.1 Study design
This is a cross-sectional pilot study describing a kidney stone's path of motion during a respiratory cycle. Stone patients were examined with an ultrasound machine capable of recording 4D footage of kidney stones. Later supplementary data was collected from patients' journals in Doculive at St. Olav's Hospital. All data was gathered at St. Olav's Hospital between August 2015 and November 2015. Below is a description of the tools used to gather and analyse data.

**3D ultrasound**
3D ultrasound and the conventional 2D ultrasound are much the same. Both rely on the same technology, using sound waves and echoes to continuously visualize the target tissue. The differences between the two methods are that in 3D ultrasound an additional spatial axis is added, making the visual output a volume rather than a picture, much like the technique computer tomography (CT). To achieve this feature the end of the 3D ultrasound probe is more rectangular, and sends out a pyramid-shape of sound waves rather than the fan-shape in 2D ultrasound probes.

The advantage of 3D ultrasound compared to the 2D ultrasound is the extra axis. With this objects that move in and out of the plane can be continuously monitored or retrieved from the recording later. A disadvantage is that all the pixels that in 2D ultrasound were used in the fan-shape are dispersed in a pyramid-shape instead. This renders the pictures less sharp, and harder to interpret, especially if the volume size is increased.

**Programs**

**DICOM converter**
This computer program has no name, and was developed by Daniel Høyer Iversen at SINTEF. It converts the DICOM-format of GE Healthcare to a standard DICOM-format which can be read by several image processing programs, for example OsiriX. Use of the converter was permitted by GE Healthcare.

**OsiriX**
OsiriX is a computer program owned by the company Pixmeo, which was created by OsiriX-creator Antoine Rosset and co-developer Joris Heuberger (100). The computer program was especially created to view images in DICOM-format (.dcm), which are the standard format for all radiology equipment (CT, magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound) (101, 102). The program can display, review, interpret and post-process diagnostic images in 2D, 3D, 4D and 5D. In this study OsiriX (version 5.5) was utilized to visualize and gain the coordinates of the kidney stones in the 4D ultrasound recordings.

**MATLAB**
MATLAB is a computer program made by MathWorks®. It has multiple areas of use; numeric computation, data analysis and visualization, programming and algorithm development, and application development and deployment (103). In this study MATLAB (MathWorks 2015) was utilized to track the kidney stones through cross-
correlation of images. The process generated coordinates with timestamps for each of the stones.

*Microsoft Excel*
Microsoft Excel is a computer program owned by Microsoft. It is a spreadsheet with features such as calculation, graphing tools, analysis options and pivot sheets (104). In this study Excel (version 2010) was used to transfer the coordinates and set up the 2D graphs.

*Geogebra*
Geogebra is a free computer program developed and owned by the International Geogebra Institute. It is a mathematical program, functioning as a geometry-, algebra- and graphing tool (105). In this study Geogebra (version 5.0.195) was utilized to set up 3D graphs displaying the kidney stones’ path of motion.

*SPSS*
SPSS is a computer program used for statistical analysis. It was developed by SPSS inc. which was bought by International Business Machines Corp. (IBM) in 2009 (106, 107).

### 4.2 Study population
The study population consisted of nephrolithiasis patients who were at St. Olav's hospital to receive ESWL-treatment at the day surgery. St. Olav's Hospital is responsible for the ESWL- and invasive treatment of kidney stone patients in the region Midt Norge, which constitutes a population of about 710,000 (108). Patients who were younger than 18 years or not able to give consent, and patients where the stone no longer remained in the kidney were excluded from the study.

A total of 20 patients were examined for the project. 5 patients were excluded because the stone had passed spontaneously, so that 15 patients were included in the study. 10 were men and 5 were women. The age stretched from 32 years to 71 years. The mean age was 57 years.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td>Fully exhaled = 0, fully inhaled = 1</td>
</tr>
<tr>
<td>Respiration frequency</td>
<td>Number (Respiration cycles per minute)</td>
</tr>
<tr>
<td>Weight</td>
<td>Number (kg)</td>
</tr>
<tr>
<td>Height</td>
<td>Number (cm)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Number (kg/m²)</td>
</tr>
<tr>
<td>Kidney anomalies</td>
<td>None = 0, kidney anomaly = 1</td>
</tr>
<tr>
<td>Lung condition affecting respiration movement</td>
<td>None = 0, reduced movement = 1, increased movement = 2</td>
</tr>
</tbody>
</table>
### Left vs right kidney
Left = 0, right = 1

<table>
<thead>
<tr>
<th>Upper vs central vs lower part of kidney</th>
<th>Lower = 0, central = 1, upper = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior vs posterior part of kidney</td>
<td>Anterior = 0, posterior = 1</td>
</tr>
<tr>
<td>Number of kidney stones</td>
<td>Number</td>
</tr>
<tr>
<td>Kidney stone largest diameter</td>
<td>Number (mm)</td>
</tr>
<tr>
<td>Kidney stone density</td>
<td>Number (HU)</td>
</tr>
</tbody>
</table>

**Table 4.1. Variables relevant to the study, and how they were noted.**

#### 4.3 Data gathering

**4D ultrasound recordings**
Nephrolithiasis patients were contacted by phone some days before their planned ESWL-treatment. The ESWL-schedule and the patients’ names and phone numbers were provided by the receptionist at the day surgery at “Gastro” centre. The patients were given a brief description of the study, and the patients who wished to participate were emailed a document containing more detailed information. Email addresses were deleted after use. Those who wished to participate, but could not provide an email address, were given time to read through the document prior to the ultrasound examination, and received a hard copy of the document. All patients had to sign the document before the ultrasound examination was conducted. The examination was done the same day shortly before the ESWL-treatment in the resting ward for pre- and postoperative patients.

The patient lay on the side with the kidney containing the stone superiorly positioned. The 4D ultrasound recordings were done with a GE Vivid E9 ultrasound machine and a GE Vivid E9 Active Matrix 4D Volume Phased Array transducer. These were retrieved from the ultrasound lab at “Acute-Heart-Lung” centre (AHL), as this was the only ultrasound machines available to student research, and brought to the day surgery at “Gastro” centre. Respiration was measured with ECG. The stone was recorded over a period of two full respiratory cycles, and several such recordings were done per patient.

**Data from patient journals**
After the ultrasound examinations were completed additional patient data were gathered from the patients’ journals in Doculive at St. Olav’s Hospital. These were weight, height, whether the patient have any kidney anomalies or lung conditions, and stone parameters (number, location, size and density).

**Confidentiality**
Each patient was assigned with a patient-ID to preserve patient confidentiality. The patient-key, connecting the patients name and birthday to the patient-ID, was stored on chief physician Carl-Jørgen Arum’s computer at St. Olav’s Hospital. The recordings and patient data were stored on a hard drive for analysis. Regional Etisk Kommité (REK) approved the study’s handling of personal information, and the study was given the REK-number: 2014/2261.
4.4 Analysis
The 4D ultrasound recordings were analysed by Sébastien Muller at SINTEF. The approach he used comprised of visualizing the stone in the program OsiriX (version 5.5), and then transfer the coordinates of the stone to MATLAB (MathWorks 2015), where he used cross-correlation to track the stones movements. The results from the analysis were relative 3D coordinates indicating the stone position at a given time in seconds. He wrote a section about how the analysis was done:

**Space and time resolution**
As the core computation is made on spatial displacement comparing volumes at different points in time, the elementary quantity evaluated is a velocity. No movement could be detected between consecutive points in time as the low velocities produced displacement below one voxel in any direction. We thus compared one volume at time t, with one volume at time t+3. The lowest possible resolution of velocity is therefore Delta(X)/3/Delta(t). The spatial resolution is anisotropic (different in every direction) and varies to some extent between patients. A typical example is taken from recording patient 16:

Time resolution Delta(t) = 0.0815 [s]
The spatial resolution is Delta(X) = [0.594 0.318 1.17] [mm]
Thus producing a velocity resolution of Delta(v) = [2.4274 1.3010 4.7984] [mm/s]

This limitation might explain why the tracking methods fails to accurately follow the changes around top inhalation and bottom exhalation as the velocities are much lower.

**Figure 4.1.** Screenshot from the program OsiriX showing a 2D image of two kidney stones from patient 10. The kidney stones are visualized as two white dots amongst the purple-dark blue background.
Figure 4.2. Screenshot from the program OsiriX showing three images of the kidney from three perpendicular planes from patient 10. The lines that make crosses over the ultrasound slices represent the different planes; the blue line is the horizontal plane, and the purple and yellow lines are the vertical planes of the ultrasound sector. The stones are only visible in the ultrasound slice in the lower left quadrant.

Muller also provided a screenshot of a time profile from patient 10 (figure 4.3) with an explanation of what a time profile is:

*Time profiles show the evolution of a physical line of space as a function of time. For example x-time profile shows an x-line at constant y and z, as a function of time. Up- and-down movement hence represents an actual movement of the anatomical structures along the x-axis. This representation is useful to control the quality of the motion tracking.*

*NB: though the profiles are originally at constant coordinates, the current version of the algorithm corrects continuously for the computed motion, thus following the anatomical volume. In mechanics, this makes the motion tracking Lagrangian rather than Eulerian.*

Muller explained the two abstract terms above during a meeting. If a subject watches moving objects the Lagrangian method of observation would be to pick an object and follow its path, while the Eulerian method involve picking a geographical spot and watching all the objects pass by.
Figure 4.3. Time profile from patient 10 showing the movements in three perpendicular directions x, y and z (noted respectively as x-time, y-time and z-time). In each graph the x-axis represents time in seconds and the y-axis represents pixel-movements.

Later the data gathered were used to:
- Make 2D graphs of movement in x, y and z directions;
- Calculate the maximum movement of the stone in x, y and z directions;
- Make 3D projections of the stone’s path of motion.

Data about the respiratory cycles were gathered from the ultrasound recordings:
- Time at start and stop for each respiratory cycle;
- Length of respiratory cycle.

5. Results
5.1 Presenting the results
Because of an analytical difficulty that will be described later (chapter 5.2), only five of the 4D ultrasound recordings were analysed. The rest of this project will only review information gathered from these five patients. The table below put values to different variables for each patient (table 5.1). Patient 16 had a history of pyelonephritis. Otherwise none of the other four had known kidney- or lung diseases that could affect the results. Unfortunately, kidney stone density was not available for any of the patients.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Nyre10</th>
<th>Nyre14</th>
<th>Nyre16</th>
<th>Nyre18</th>
<th>Nyre19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>♂</td>
<td>♂</td>
<td>♀</td>
<td>♂</td>
<td>♀</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65</td>
<td>71</td>
<td>65</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Largest diameter (mm)</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Number of kidney stones</td>
<td>2</td>
<td>≥ 5</td>
<td>1</td>
<td>≥ 5</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Anterior vs. posterior kidney</td>
<td>Anterior</td>
<td>Posterior</td>
<td>Posterior</td>
<td>Anterior</td>
<td></td>
</tr>
<tr>
<td>Lower vs. central vs. upper kidney</td>
<td>Lower</td>
<td>Upper</td>
<td>Kidney pelvis</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Left vs. right kidney</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24,8</td>
<td>28,1</td>
<td>24,7</td>
<td>23,8</td>
<td>22,2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1,85</td>
<td>1,79</td>
<td>1,57</td>
<td>1,80</td>
<td>1,67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85</td>
<td>90</td>
<td>61</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td>Respiration frequency (per minute)</td>
<td>16</td>
<td>19</td>
<td>11</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 5.1. Values of variables in patients 10, 14, 16, 18 and 19 gathered from Doculive at St. Olav’s hospital.

The results from the analysis were used to plot 2D graphs (figures A.1-A.5), as the one from patient 19 seen below (figure 5.1). These show the stones’ movements in millimetres in three perpendicular directions called x, y and z as functions of time in seconds. X, y and z may be converted into directions that resemble those physicians use when describing locations in the body. X would translate to the cranial-caudal axis, y to the lateral-medial axis, and z to the ventral-dorsal axis. Whether the movement is positive or negative is decided by which kidney is analysed (the right or the left) and if there was any mirroring during the recording and/or the analysis (table 5.2). False mirroring of the ultrasound image could have occurred if different ultrasound settings were used without the operator being aware of that, for example changing between heart and abdominal ultrasound-settings. Ideally, the table below would be representative. Unfortunately, the mirroring makes it hard to tell what the positive and negative numbers represents. However, through studying the ultrasound recordings visually the kidney stones move caudally and ventrally during inspiration, and cranially and dorsally during exhalation. The stones generally have little or no movement along the lateral-medial axis.
Figure 5.1. Showing a 2D graph of kidney stone movements in patient 19 made in Microsoft Excel. Curves x, y and z represent three perpendicular directions. X-axis represent time in seconds and y-axis represent absolute movement in millimetres. Note a cyclic movement in x and z directions, while there is seemingly non in y direction.

<table>
<thead>
<tr>
<th>Positive direction</th>
<th>Negative direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial</td>
<td>Lateral</td>
</tr>
<tr>
<td>Cranial</td>
<td>Caudal</td>
</tr>
<tr>
<td>Dorsal</td>
<td>Ventral</td>
</tr>
</tbody>
</table>

Table 5.2. Showing which direction is positive and negative in a non-mirrored ultrasound recording.

The graphs were used to acquire maximal movement in millimetres in each direction. These are shown in the table below (table 5.3).

<table>
<thead>
<tr>
<th>Directions</th>
<th>Patient 10</th>
<th>Patient 14</th>
<th>Patient 16</th>
<th>Patient 18</th>
<th>Patient 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>6,7</td>
<td>6,8</td>
<td>2,4</td>
<td>4,7</td>
<td>8,6</td>
</tr>
<tr>
<td>y</td>
<td>0,5</td>
<td>1,1</td>
<td>1,8</td>
<td>0,4</td>
<td>0,4</td>
</tr>
<tr>
<td>z</td>
<td>14,8</td>
<td>9,3</td>
<td>4,6</td>
<td>7,0</td>
<td>10,0</td>
</tr>
<tr>
<td>Total</td>
<td>15,6</td>
<td>9,4</td>
<td>4,6</td>
<td>7,6</td>
<td>12,3</td>
</tr>
</tbody>
</table>

Table 5.3. Showing maximal distance in millimetres between the two points furthest apart in the stone’s path of motion in patients 10, 14, 16, 18 and 19.

3D coordinates of the stone during one respiratory cycle from each patient are represented in 3D illustrations of the kidney stones’ trajectories (figure A.6-A.10). The program Geogebra was utilized (105). The coordinates were converted so that all curves...
start in origo (0, 0, 0). Each point used to make the curve was marked with a letter to separate different curves, and the time at which the stone centre was at that location in milliseconds. An example from patient 10 is seen below (figure 5.2).

![3D graph showing the kidney stone's path of motion in patient 10. Each point is marked with a letter indicating which patient it is, and numbers representing time in milliseconds. The unit of the three axes x, y and z are millimetres.](image)

The start- and stop times and time length of the respiratory cycles of each patient were obtained from studying the ultrasound recordings, and are listed in the table below (table 5.4). In patients 14, 16, 18 and 19 the start and stop of each respiratory cycle correspond to the oscillations of the x and z curves.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Respiratory cycles’ start and stop times (s)</th>
<th>Length of respiratory cycles (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 10</td>
<td>First 3,0 - 6,7</td>
<td>3,7</td>
</tr>
<tr>
<td></td>
<td>Second 6,7 - 10,4</td>
<td>3,7</td>
</tr>
<tr>
<td>Patient 14</td>
<td>First 1,1 - 4,2</td>
<td>3,1</td>
</tr>
<tr>
<td></td>
<td>Second 4,2 - 7,5</td>
<td>3,3</td>
</tr>
<tr>
<td>Patient 16</td>
<td>First -0,2 - 5,1</td>
<td>5,3</td>
</tr>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Patient 18</strong></td>
<td>0,0 - 4,1</td>
<td>4,1</td>
</tr>
<tr>
<td></td>
<td>4,1 - 8,2</td>
<td>4,1</td>
</tr>
<tr>
<td><strong>Patient 19</strong></td>
<td>1,0 - 5,4</td>
<td>4,4</td>
</tr>
<tr>
<td></td>
<td>5,4 - 9,7</td>
<td>4,3</td>
</tr>
</tbody>
</table>

**Table 5.4.** *Showing the start and stop times and time length of the first and second respiratory cycles in each patient. In patient 16 the respiratory cycle started 0,2 seconds before recording began, and so the time has a minus in front.*

### 5.2 Limitations to the analysis method and solutions to these

Muller described how cross-correlation was used to analyse the ultrasound recordings, and the problems this caused when the stone moved less than \[2.4274 \ 1.3010 \ 4.7984\] (mm/s). In other words, if there was less than 4,8 mm movement in z direction in 1 second this would not have been registered. This applies through the entire recording. For example, in a recording of 6 seconds where the stone moves at a constant rate of 4,0 mm/s in z direction the stone’s true movement in the end is 24 mm, but would be registered as the stone being still the entire time. However, velocity of 4,8 mm/s or more will be presented quite accurately (figure 5.3). Typically, this limitation will affect the measurement of distance at the top of the respiration curve, where the patient goes from actively inhaling to passively exhaling, and at the end of the respiratory cycle, where the patient pauses before the next cycle. This probably explains why the z and x curves tend to have a square appearance, rather than a more continuous smooth curve.

Unlike the registration of movement in z direction, the registration in y direction might be too accurate, considering it requires only 1,3 mm of movement per second. Most likely some of the movement registered in y direction is attributed to noise. This means there in reality is even less movement along this axis, rendering it to practically no movement at all.

If one wants better registration of movement, the graphic display resolution could be increased by adding more pixels in the directions of interest. In this study one could rearrange the pixel-structure that the ultrasound machine produces, adding more to the x and z direction, and removing some from the y direction, because movement in this direction is approximately equal to 0, and therefore is of little interest.
Figure 5.3. Graph showing hypothetical representation of a kidney stone’s motion. Actual movement is the green curve and registered movement is the pink curve.

The reason the 10 other recordings could not be analysed was because a too narrow sector had been recorded. In cross-correlation one image is compared to another to find the best possible overlap. When this is found the gap between the two images is measured to find the distance an object has moved. This method therefore requires not only the stone, but also a zone around it to be recorded. Unfortunately, only five recordings met these standards. To improve the quality of the measurement a larger zone should be used, because then there is less chance of choosing the wrong overlap. A smaller zone will of course increase the risk of choosing the wrong overlap, and you may get artefacts. Two of these can be seen in figure A.3 at 0 and 5 seconds.

5.3 Statistical analysis of the results
Correlation analysis was used to determine the reproducibility of the measured stone movements. In correlation one finds the two points in time where the curves have the best possible overlap, and calculate how well the curves trace one another. Two different types of correlations were used. Pearson correlation is a non-parametric linear method of correlation, while Spearman correlation is a parametric non-linear method. There are disadvantages to both, as Pearson’s method only will detect linear relationships, and Spearman’s method does not measure exact values, but rather whether the coordinates increase or decrease together. The optimal solution would have been to use a non-parametric and non-linear correlation method, but as of today these
are still in the making (109), so a compromise will be to use both. The methods calculate correlation coefficients in the range -1 to +1, where below 0 is negative correlation, above 0 is positive correlation and 0 is no correlation.

One could not use correlation to look at the 3D trajectory of the stone. This was due to the phase shift, where the top of the X and Z curves occur at different times, and the fact that the recordings consist of only two respiratory cycles. If one was to assess the 3D trajectory, the phase shift and short recording time would lead to no correlation found even if there actually was perfect correlation. This because only one curve belonging to one of the three axes would have had perfect correlation at a particular time, while the two remaining axes would have had too few coordinates to provide good correlation. To avoid this each axis was assessed separately, where the coordinates were divided at the most appropriate time to check correlation. This process was done in MATLAB (appendix D), while Pearson’s and Spearman correlation were done in SPSS, all provided by Sébastien Muller. There was minimal movement along the y-axis, and so it would be meaningless to assess the correlation for this curve. The correlation coefficients with p-values are listed in the table below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pearson’s correlation</th>
<th>Spearman correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x-axis P-value</td>
<td>z-axis P-value</td>
</tr>
<tr>
<td>Patient 10</td>
<td>0,792*</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Patient 14</td>
<td>0,585*</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Patient 16</td>
<td>0,941#</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Patient 18</td>
<td>0,743*</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Patient 19</td>
<td>0,239</td>
<td>0,137</td>
</tr>
</tbody>
</table>

Table 5.5. Correlation coefficients and P-values for the x- and z-axes displaying correlation between the kidney stones’ movements during the 1. and 2. respiration cycles. * marks statistically significant correlation coefficients. # marks a special case where the 2. x-curve was linear.

Looking at the table 5.5 one can see that all correlation coefficients are positive. Positive correlation in Pearson’s method indicate both curves are climbing, while in Spearman’s method it signifies that both curves are either rising or falling together. Patient 10, 14 and 16, with one exception, all have significant correlation for x- and z-curves. The x-curve of patient 14 does not give a certain correlation with Spearman’s method because the curves do not rise together. Still, both curves begin and end at approximately the same level. Neither Pearson’s or Spearman’s method give certain correlation in the z-curve of patient 18 and the x-curve of patient 19. Studying the correlation graphs (figure A.18-A.19) one of the curves are broader and taller than the other. This might be due to variations in respiration depth and frequency, or limitations in the analysis method (chapter 5.2). Reviewing all correlation graphs (figure A.11-A.20) all curves, whether they have significant correlation or not, display an apparent resemblance considering curve-shape.
Figure 5.4. The stone movements along the x-direction (left) and the z-direction (right) from patient 18 is represented in the graphs above. These correlation graphs show extracted parts from the 2D graphs of either the x- or z-curve. The parts of the curve wherein the stone moves the most per unit time are put on top of each other to display the correlation between them. The blue and green curves are movement during the 1. and 2. respiratory cycles respectively. The x-axis represents time, and the y-axis physical movement.
6. Discussion

6.1 Interpretation of the results

Three questions were of importance in this study, and are significant within ESWL-treatment;

- How, in a 4D perspective, does a kidney stone move?
- During the respiratory cycle, at what point if any does the stone remain stationary the longest?
- Does the stone follow a repetitive pattern of motion?

The point behind the first question is to see whether there are any interindividual similarities considering kidney stone trajectories. Figures A.1-A.5 and table 5.3 show that the stone’s movements in direction y are negligible, meaning the stones’ paths of motion are confined to only one plane. This information is supported by what has previously been documented (chapter 3) and what was observed when the ultrasound recordings were made. For the most part one could follow the stones’ movements through an entire respiratory cycle with only 2D ultrasound. Put in a practical setting this means that 2D ultrasound probably is adequate to track the kidney stones during ESWL treatment. Still, 3D ultrasound makes it easier to find and keep the kidney stone within the tracking area, and will be needed in cases where the stone moves in all three directions (chapter 3).

The stones move primarily along the ventral-dorsal- and the cranial-caudal axes. Total measured movement varies between approximately 5-15 millimetres. Still, the analytical method might not have measured the full distance, meaning the total movement in reality might be greater. The total measured distance also varies between the five patients, and so one can expect that there exists a greater variance in a larger population. In other words, continuous tracking of the kidney stones during treatment is probably advantageous, especially with greater displacement.

What the second question really asks is; when would it be best to shoot the stone? A moving target is a lot more difficult to hit than a stationary one. This study suggests that the most appropriate time to shoot the stone is at the end of exhalation. At this point the stone movements are minimal compared to during inhalation and the first part of exhalation. This was directly observed during ultrasound examinations. Figure 6.1 demonstrates the same, as the stone spends most of the time at the end of the respiratory cycle. This is visualised better by plotting all coordinates that make up the curve because most of the coordinates will gather at the end of the curve.
The essence behind the third question is to figure out whether the ESWL-machines aim has to be adjusted frequently to focus on the stone. If kidney stones were to move in the exact same pattern every respiratory cycle, the aim can be set on a certain area, and one will not have to readjust it unless the patient moves. Information on stone trajectories together with the real-time 3D ultrasound tracking development (chapter 3) might lead to 100% of the shock waves striking the kidney stone during ESWL-treatment. If the opposite were true, the aim would have to be adjusted after every new respiratory cycle. This study cannot fully answer this question. One reason is the limited patient data. There were both too few cases and not enough respiratory cycles in each recording to study the path of motion in detail. Another reason is the accuracy of the analytical method. The velocity had to be equal to or larger than 2,4 mm/s in x direction and 4,8 mm/s in z direction to be registered. This is a too great margin of error, which will have to be reduced. The ultrasound recordings show promise, as the stone seems to be moving in a repeating pattern. However, the same outcome could not be demonstrated in the analysis of the recordings (figure 6.2). Further investigation on the matter, where the pixel-structure is changed and more patient data is recorded, is required.
6.2 ESWL-treatment today
Currently ESWL is the most common choice of treatment while URS is the second most common. Comparing the two treatment options there are several advantages and disadvantages in both. The main advantage of ESWL is that it is non-invasive and thereby more convenient and less complicated for the patient. Patients receiving ESWL experience less postprocedural symptoms such as flank pain, dysuria and hematuria. There are also less complications and auxiliary procedures following ESWL treatment. As URS is an invasive procedure the patients must spend more time in hospital and more time to recover. The benefits to URS are a higher stone-free-rate and fewer retreatment sessions than ESWL. Health costs are difficult to assess, as they will vary with number of retreatment sessions, auxiliary procedures and days in hospital (110).

ESWL is non-invasive and should be the preferred treatment. 80-90% of nephrolithiasis patients are suitable for ESWL-treatment (111, 112), but a large fraction of the patient-group does not get this treatment. At St. Olav’s hospital in Trondheim the trend since 2010 have been to treat between 50-60% of nephrolithiasis patients with ESWL (figure 6.3 and table 6.1).
Figure 6.3. Data regarding numbers treated for kidney stones from St. Olav’s hospital in Trondheim.

Table 6.1. Distribution between different treatment modalities per year. Data from St. Olav’s hospital in Trondheim.

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESWL</td>
<td>57.6%</td>
<td>57.9%</td>
<td>56.8%</td>
<td>53.8%</td>
<td>63.7%</td>
<td>53.3%</td>
</tr>
<tr>
<td>URS</td>
<td>32.0%</td>
<td>31.5%</td>
<td>32.1%</td>
<td>33.0%</td>
<td>26.4%</td>
<td>37.2%</td>
</tr>
<tr>
<td>PCNL</td>
<td>10.2%</td>
<td>10.7%</td>
<td>10.8%</td>
<td>8.6%</td>
<td>9.1%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Åpen/laparoskopi sk operasjon</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

There are probably several aspects that influence the urologists’ decision upon treatment method. One aspect is treatment success. As mentioned earlier stone factors decide the success rate of ESWL. Stones larger than 10 mm in diameter, stones with high density or stones located to the lower calyces are less likely to be crushed and later expelled with ESWL (113). Patient factors such as BMI above 30 kg/m² also decrease ESWL success rate (114). Stones or patients in these categories might be treated with URS instead because evidence shows higher success rates.

Another aspect is the quality of the treatment method. In the current technique pulses are focused at a point in the kidney stones trajectory and the lithotriptor is set to fire at a constant rate to hit the stone as it passes by. In other words, few of the pulses actually hit the stone. Instead the pulses potentially injure surrounding tissue making the procedure painful and increasing the risk of complications (62). To decrease the treatment of surrounding tissue the focal point can be reduced, but this makes it even harder to hit the stone, and often requires more retreatment sessions. ESWL, though it is the best treatment as of today, is not an optimal treatment because of the periprocedural kidney stone tracking, and has room for improvement.
A third aspect is economy. An ESWL-machine is a large investment for a hospital. St. Olav’s hospital bought a new machine in 2015 which cost about 3.5 million NOK (62). Not all small hospitals can afford that, and not all patients are willing to travel long distances to a larger hospital, especially if it is a good possibility that he or she will need a retreatment as well.

All these aspects and more contribute to the distribution between different treatment options seen today. As discussed in the epidemiology section more people develop the disease and will need treatment in the future. Hopefully better visualisation of the stone and shooting only when the stone is in focus will make ESWL the preferred option in more nephrolithiasis patients, sparing the patients for unnecessary pain and the society for extra costs.

7. Conclusion

4D movement
From the information, tables and graphs above (tables 5.2-5.4 and figures 5.1-5.2) the kidney stones move ventrally and some caudally during inspiration, but usually have minimal movement along the medial-lateral axis. The stones move quickly along the trajectories, and then seem to move very little at the end of exhalation.

Studying table 5.3 all ultrasound recordings show greatest stone displacement along the ventral-dorsal axis of the body. This is probably due to the shape of the lungs and diaphragm, as the structures protrude further caudally at the dorsal side compared to the ventral side. During the breathing cycle the abdominal organs, including the kidneys, are displaced ventrally as the lungs are expanded. There is also displacement caudally, but this is generally less than the displacement ventrally (table 5.3). Total measured movement varies between approximately 5-15 mm.

Respiration
The stones’ movements correlate fairly well with the respiration cycles. In the 2D graphs (figure A.1-A.5) one can see that the movement along x and z directions independently have cyclic patterns. The start and stop times in table 5.4 correlate well with the 2D graphs in patients 14, 16, 18 and 19. In all these graphs there are at least two tops interspaced by a longer period with no top or a sleek rising. Again this points to little or no movement at the end of exhalation, which could be called the stone’s “resting position”. In patient 10 the recording is not long enough to span two full respiratory cycles, and so one cannot tell how well it correlates.

Interindividual- and kidney stone variables
Considering most of the ultrasound recordings could not be analysed, comparing the few remaining recordings with the interindividual- and kidney stone variables is pointless. However, they are still included in the results to show that the five patients were comparable in all parameters.
Reproducibility

Though 5 patients are a very low number there is a striking similarity between the 2D graphs (figure A.1-A.5), both because of the little movement in the lateral-medial axis and due to cyclic movements correlated to respiration. The 3D curves (figure A.6-A.10) on the other hand seem to look quite different, with the exception that none of them, like the 2D graphs, have much movement in the lateral-medial axis. However, if one considers that some of the graphs are upside down (chapter 5.1), that the registration at low speeds is somewhat limited (chapter 5.2), and that there are artefacts (chapter 5.2), some similarities become clearer. All stones in the 3D graphs start in origo, travel some millimetres to a turning point, and then almost return back to origo. This gives the impression that the stones follow an ellipsoid curve. If the stones where to return to the starting position after exhalation the ellipsoid curve would have been a fact. Unfortunately, it could not be demonstrated in the analysis. Still, it was observed during the recording of the kidney stones. The stones returning to the starting position would also be likely considering they often are fixated in the kidney, and thereby follow the kidneys’ movements.

The statistical analysis shows a significant correlation between 1. and 2. respiratory cycles for at least one direction in all patients (chapter 5.3). The reason some graphs could not demonstrate significant correlation were likely due to the variations in the patients’ depth and frequency of respiration, and because the recordings contain too few respiratory cycles. By adjusting the recording method and adding more patients to the study one might come closer to verifying reproducibility.

Relation to ESWL-treatment

All the results from this study and literature on the subject indicate that 2D ultrasound is often sufficient for tracking the kidney stone during ESWL-treatment. Still, 3D ultrasound may perform superiorly in cases where the stone moves in all three directions, so that the tracking-system can continue working and be able to aim at the stone. Maximizing the actual number of stone hits by energy pulses could be achieved by only applying energy when the stone is in the “resting position”, being the location of the stone at the end of exhalation, as this is when the stone moves the least. The reproducibility of the stones’ trajectories is still uncertain. If the stones’ trajectories follow a certain pattern tracking of the kidney stones might get a lot easier, as one will have an educated guess as to where the stone will move next. Information on stone trajectories together with the further development of real-time 3D ultrasound tracking might lead to 100% of shock waves striking the stone, so that none strike surrounding kidney tissue.
8. Bibliography


36. Zarse CA, Hameed TA, Jackson ME, Pishchalnikov YA, Lingeman JE, McAteer JA, et al. CT visible internal stone structure, but not Hounsfield unit value, of calcium oxalate


107. Dicolo JA. IBM to Acquire SPSS, Adding to Acquisitions. 2009 30 July.


9. Appendices
Appendix A. 2D-, 3D- and correlation graphs

2D graphs

**Patient 10**

![2D graph - patient 10](image)

**Figure A.1. 2D graph – patient 10.**

**Patient 14**

![2D graph - patient 14](image)

**Figure A.2. 2D graph – patient 14.**
Figure A.3. 2D graph – patient 16.

Figure A.4. 2D graph – patient 18.
Figure A.5. 2D graph – patient 19.

Figure A.6. 3D graph – patient 10.
Figure A.7. 3D graph – patient 14.
Figure A.8. 3D graph – patient 16.
Figure A.9. 3D graph – patient 18.
Figure A.10. 3D graph – patient 19.
Correlation graphs

Figure A.11. Correlation graph for x-axis – patient 10.

Figure A.12. Correlation graph for z-axis – patient 10.
Figure A.13. *Correlation graph for x-axis – patient 14.*

Figure A.14. *Correlation graph for z-axis – patient 14.*
Figure A.15. Correlation graph for x-axis – patient 16.

Figure A.16. Correlation graph for z-axis – patient 16.
Figure A.17. Correlation graph for x-axis – patient 18.

Figure A.18. Correlation graph for z-axis – patient 18.
Figure A.19. Correlation graph for x-axis – patient 19.

Figure A.20. Correlation graph for z-axis – patient 19.
Appendix B. Research information and compliance form – 01.12.14

Forespørsel om deltakelse i forskningsprosjekt

Analyse av nyresteiners bevegelse

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å kartlegge nyresteiners bevegelse. Du har fått denne forespørselen fordi du har symptomgivende nyrestein som er behandlingskrevende. Denne studien blir gjort som del av en hovedoppgave ved NTNU i samarbeid med St. Olavs hospital.

Hva innebærer studien?


Mulige fordeler og ulemper


Hva skjer med ultralydopptakene og informasjonen om deg?

Ultralyd-opptakene og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjenningende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Opplysningene om deg vil bli lagret i en database på en datamaskin på St. Olavs hospital i 5 år. Etter dette vil navnelisten ødelegges slik at alle opplysninger avidentifiseres på permanent basis. Ultralyd-opptakene og de tilhørende pasientopplysningene vil bli avidentifisert og overført til den større studien RASMUS ved institutt for teknisk kybernetikk NTNU.
Det vil ikke være mulig å identifisere deg i resultatene av denne studien når disse publiseres.

**Frivillig deltakelse**

**Ytterligere informasjon om studien finnes i kapittel A**
**Ytterligere informasjon om personvern, økonomi og forskning finnes i kapittel B**
**Samtykkeerklæring følger etter kapittel B**
Kapittel A – Utdypende forklaring av hva studien innebærer

Kriterier for deltakelse
Alle nyresteinspasienter som skal til ESWL-behandling vil bli spurt om deltakelse i denne studien.

Bakgrunnsinformasjon om studien
Dagens nyresteinsbehandling er ikke optimal da pasienter ofte må inn til rebehandling eller får komplikasjoner etter behandlingen. RASMUS er et doktorgrads prosjekt som vil videreutvikle og forbedre dagens nyresteinsbehandling. Til dette prosjektet trengs opplysninger om nyresteiners bevegelse i ulike pasientgrupper. Denne studien vil kunne bidra med denne informasjonen ved å undersøke en gruppe nyresteinspasienter med 3-D ultralyd.

Undersøkelse
Ultralyd-undersøkelsen vil bli gjort med pasienten liggende i sideleie på undersøkelsesbenk med en pute under seg. Ultralydgel vil bli brukt for optimal kontakt mellom ultralydproben og pasientens hud. Hvis det blir funnet anomalier under undersøkelsen vil behandlende urolog bli informert om dette med henblikk på eventuell videre utredning.

Kapittel B – Personvern, økonomi og forskning

Personvern
Opplysninger som registreres om deg er:

- Respirasjonsfrekvens
- Vekt
- Høyde
- Lungetilstander som påvirker respirasjonsbevegelser
- Nyreanomalier som påvirker nyrens bevegelse
- Nyresteinens lokalisasjon, antall, hardhet og størrelse

Andre forskere vil ha tilgang til ultralyd-opptakene og opplysningene over etter at de er blitt aidentifieret.
Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at undersøkelse og aidentifiserte opplysninger utleveres til institutt for teknisk kybernetikk ved NTNU.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien er finansiert gjennom forskningsmidler fra NTNU. NTNU dekker veiledning og kurs for medisinstudenten, samt kostnader knyttet til publisering.

Forskning
Dette er en hovedoppgave for en medisinstudent ved NTNU, og informasjonen skal videre brukes i en doktorgrad ved NTNU. Studien er godkjent av Regional Etisk Komité.

Informasjon om utfallet av studien
Som deltaker i studien har du rett til å få informasjon om resultatet av studien.
Samtykke til deltakelse i studien
Jeg er villig til å delta i studien:_________________________________________________
(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien:_____________________________________
(Signert, rolle i studien, dato)
Appendix C. Omitted sections
These are the original sections covering nephrolithiasis epidemiology and risk factors. They were excluded from the project as they contained too many citations.

C.1 Epidemiology
Kidney stone disease (nephrolithiasis) is a common disease that through the last decades has become even more common. The changes in American epidemiology were examined in a nationwide study based on National Health and Nutrition Examination Survey II (NHANES II) and NHANES 2007-2010. The results showed a marked increase in prevalence, as the disease had gone up from 3.2% in the period 1976-1980 to 8.8% in the period 2007-2010 (1, 2). Europe seems to be following the same trend. An Italian study of the population in Rome showed increasing prevalence from 11.7 to 17.2 out of 1000 inhabitants in the period 1983 to 1993-1994 (3). Data collected from the United States, Germany, Sweden, Italy and Spain indicate a general increase in the population (4). The number of incident kidney stone cases is also rising in children globally (5-8).

The incidence of nephrolithiasis is distributed unevenly within the countries’ populations in respect to gender, age and climate. 40 years ago 3 times more men than women were diagnosed with nephrolithiasis in the United States. Recently this has changed as the incidence in men has dropped, except for the 70 years plus group, while the incidence in women has risen. Now the men-women ratio is 1.3, meaning men only have a slightly higher risk of nephrolithiasis compared to women (9). In some countries women are also more likely to develop stones than men, but often the difference between genders is minimal (4).

The stone formation rate is also age-dependent. Many countries share similar incidence-curves for the two sexes and different age groups. The incidence in men starts to increase at 20 years, peaks between 40-60 years, and declines rapidly after 70 years of age. Women start and stop developing kidney stones at the same ages as men do. However, the incidence is somewhat lower and quite stable. Additionally the women’s curves have one or two minor peaks. If there is only one it is usually at 50-70 years of age. When there are two the extra peak is in the late twenties to early thirties (4, 9).

Generally there seems to be a connection between warmer climates and kidney stone disease. This is the case both in countries with constantly hot climates and countries that only experience hotter seasons. A large American study found twice as high prevalence in southeast regions of the United States compared to the northwest regions (10). This will be further discussed in the paragraphs containing risk factors.

C.2 Risk factors
Lately several studies have been conducted to identify risk factors of nephrolithiasis. The main goal has been to understand the epidemiology and pathophysiology, and by that finding means of treating and preventing the disease. Some of them will be discussed below.

Obesity
Many studies have concluded that obesity is a major risk factor of nephrolithiasis (11-14), where obese patients are defined as having a Body Mass Index (BMI) of 30 kg/m² or more (15). The wave of obesity in developed countries may in fact be one of the main
reasons for the rising incidence of kidney stone disease. This is what Taylor et al. found as they analyzed three large cohort studies (12), the Health Professional Follow-up Study (HPFS), the Nurses’ Health Study I (NHS I) and the Nurses’ Health Study II (NHS II).

Increasing weight is a risk factor in both genders, but there is a stronger relationship between obesity and kidney stone disease in women than in men (12, 14, 16). Some researchers have suggested this might be because of women’s higher percentage of body fat. The shifting gender ratio amongst nephrolithiasis patients observed the last decade (14) might be explained by this hypothesis and the fact that more women than men are obese globally these days (15).

One study have found that the risk of nephrolithiasis does not increase any further in high-BMI versus low-BMI obese patients (13). A newer study divided both non-obese and obese patients in BMI-groups to study BMI as a continuous variable. They discovered that patients with high BMI values are at greater risk compared to patients with low BMI values, and that this applies to non-obese patients as well (12).

A high BMI value has been associated with higher urinary concentration of sodium, uric acid and oxalate, and low urinary pH in both genders (17, 18). In clinical studies obesity has been related to uric acid- and calcium oxalate stones, but not to calcium phosphate stones (19). Calcium excretion-levels in the proximal tube of the kidney rise with increasing sodium excretion-levels. The resulting hypercalciuria most likely contribute to calcium oxalate nephrolithiasis in patients (20, 21). Researchers believe the connection between uric acid nephrolithiasis and obesity to be mediated by insulin resistance. Insulin resistance is related to impaired ammoniagenesis in the kidney, lowering the urine pH, and thereby increasing supersaturation of uric acid (18, 22, 23).

In addition to being a risk factor itself, obesity raises the risk of several other conditions associated with nephrolithiasis; hypertension, atherosclerosis, diabetes mellitus type II, metabolic syndrome and gout (22, 24-29).

**Diet and fluid intake**

According to several studies certain foods and beverages influence the risk of kidney stone formation. Calcium and its connection to nephrolithiasis have been of particular interest to scientists. Some studies have concluded that taking supplementary calcium increases the risk of developing calcium oxalate stones, whereas increasing dietary calcium actually reduces the risk (30, 31). Other studies have found that supplementary calcium has no effect on kidney stone formation (32, 33). The divergent results might be explained by the timing of calcium ingestion. Dietary calcium consumed together with oxalate will become an insoluble salt, which will prevent both substances from being absorbed by the intestines. Supplementary calcium taken outside meals will not decrease the risk, but might in fact increase it. This would also explain why increasing calcium intake has little effect on calcium excretion (34).

Too little fluid intake is considered an important risk factor of nephrolithiasis. The amount of fluid someone drinks during the day decides urinary output. A low urinary output gives less volume to dilute substances, and the higher the concentration of substances is the more likely they are to supersaturate. In the HPFS and NHS I and II
Fluid intake was inversely correlated to risk of nephrolithiasis (31-33). As a consequence EAU guidelines recommend that nephrolithiasis patients drink at least 2.5 litres of fluid every 24 hours (35).

Stone patients are advised to reduce their consumption of sodium chloride, animal protein and oxalate. As mentioned earlier sodium influence the excretion of calcium, and is believed to contribute to kidney stone formation. Animal protein changes the urines composition of calcium, citrate, uric acid and oxalate, and it lowers the urines pH. The change increases the supersaturation of uric acid and possibly calcium oxalate, and leads to an increase in stone formation (36, 37). Oxalate is thought to play a minor role in stone formation. This is because urinary oxalate levels rarely are high as most foods contain very small amounts of oxalate, and oxalate absorption is strongly associated with dietary calcium (30-33). Reduced oxalate intake is only advised if it is already excessive (35).

**Family history**

In several studies kidney stone formation is significantly increased amongst people with a positive family history compared to people with no such history. The HPFS examined a population of 37,999 male participants in 1986, where 7.8% were patients who had been diagnosed with kidney stones (Figure 2.1) (38). In the kidney stone patients’ group 17.2% had a parent or sibling who had suffered the same disease, whilst only 6.4% of controls had a positive family history. After 8 years of follow-up 795 incident cases of nephrolithiasis had occurred in the control group, where 203 of them were patients with nephrolithiasis in the family. The relative risk of developing the disease in patients with family history of nephrolithiasis was estimated to 2.57 (95% CI, 2.19 to 3.02). Other studies have found that approximately 14% (39) to 37% (40) of stone patients have at least one first-degree relative with nephrolithiasis, compared to only approximately 5% to 22% in healthy controls (39, 41, 42).

The nephrolithiasis patients with a positive family history are more prone to be diagnosed with kidney stones at an earlier age, and to have more stone episodes and recurrent stone disease (43, 44).

Though nephrolithiasis clusters in families, less than 1% of cases are attributed to monogenic inheritance. Most probably polygenic inheritance, environmental factors or both predispose individuals in kidney stone families to develop the disease. Some
hereditary traits associated with stone formation are hypercalciuria (45), defect oxalate transport (46), incomplete tubular acidosis (47), and increased uric acid production (48). Environmental factors may be diet or fluid intake as discussed above.

**Warm environment**

Living or working in warm environments have been linked to development of kidney stones. This link is most likely mediated by dehydration causing low urinary output. A study of workers in a steel factory revealed that those assigned to the hot areas had a nine-fold increase in kidney stone prevalence compared to their companions working in room temperature (49). In Italy and the US studies have reviled a higher prevalence of kidney stone disease among the southern population compared to the northern one (3, 10), and during the warmer months of the year more Italians and Americans visit the emergency department because of renal colic (50, 51).

C.3 Bibliography


Appendix D. MATLAB autocorrelation code

clear; clf;

A = csvread('patient5.csv');
[N,tull] = size(A);
corr_coef = zeros(2*N-1,1);
idx = zeros(1,3);
vnd_m = floor(0.3333*N);
vnd_M = floor(0.6667*N);
figure(1);
for i=1:3;
    X = A(:,i);
    [r, lags] = xcorr(X,X);
    corr_coef = r/var(X)/N;
    plot(1:N,corr_coef(1:N),'.-'); grid on; hold on;
    idx(1,i) = find(corr_coef == max(corr_coef(vnd_m:vnd_M)));
end

n = floor(N/2);
% figure(2);
% for i=1:3
%     subplot(3,1,i); plot(1:33,A(1:33,i),1:47,A(33+1:N,i));
%     % Naar lag er 47 = 80-33
% end

% corrmax = max(r)/var(X)/length(X)