|  |
| --- |
| Promotor: Karl Martin Wissing, MD, PhD Co-promotor: Els Van de Perre, MD |
| Geneeskunde en Farmacie |

|  |
| --- |
| Proef ingediend met het oog op het behalen van de graad van Master in de Geneeskunde |
| **KIDNEY STONE PREVENTION** |
| **Effect of kidney stone prevention on urinary risk factors for kidney stone formation and new stone formation: a single centre retrospective cohort study** |
| **Florine janssens****2020-2021** |

TABLE OF CONTENTS

[ABSTRACT 3](#_Toc70238540)

[ABBREVIATIONS 4](#_Toc70238541)

[INTRODUCTION 5](#_Toc70238542)

[PATIENTS AND METHODS 13](#_Toc70238543)

[1. OVERALL STUDY DESIGN 13](#_Toc70238544)

[2. TREATMENT PROTOCOL OF THE KIDNEY STONE PREVENTION CLINIC 13](#_Toc70238545)

[3. DATA RETRIEVAL 14](#_Toc70238546)

[4. EVALUATION OF URINARY RISK FACTORS 17](#_Toc70238547)

[5. DETERMINATION OF THE PRE- AND POSTTREATMENT RATES 18](#_Toc70238548)

[6. DEFINITIONS 21](#_Toc70238553)

[7. STATISTICAL ANALYSIS 22](#_Toc70238556)

[8. ETHICS 23](#_Toc70238560)

[RESULTS 24](#_Toc70238561)

[1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION 24](#_Toc70238562)

[2. PRE-TREATMENT FINDINGS 28](#_Toc70238566)

[3. POST-TREATMENT FINDINGS 35](#_Toc70238569)

[DISCUSSION 40](#_Toc70238572)

[CONCLUSION 48](#_Toc70238573)

[ACKNOWLEDGEMENTS 49](#_Toc70238574)

[REFERENCES 50](#_Toc70238575)

[ATTACHMENT 1: stone compositions according to the European Renal Stone Network Survey 55](#_Toc70238577)

[ATTACHMENT 2: ICH GCP certificate 55](#_Toc70238578)

[ATTACHMENT 3: approvals of the Ethics committee 56](#_Toc70238579)

# ABSTRACT

**Objective**- Nephrolithiasis is an increasingly prevalent and highly recurrent condition. The role of individual preventive measures in preventing recurrence has been established by several randomized controlled trials. However, there is a lack of studies demonstrating the efficacy of combined preventive measures. This single centre retrospective cohort study evaluated the influence of combined preventive measures on the urinary risk factors for kidney stone formation, symptomatic renal colic rate, kidney stone formation rate and rate of performance of urological procedures.

**Patients and methods**- Data of nephrolithiasis and nephrocalcinosis patients attending the Kidney stone Prevention clinic (UZ Brussel) between 22/12/2004 and 31/12/2020 were collected in a database. Retrospective cohort analysis was performed by means of a Wilcoxon signed rank test to compare pre- and posttreatment urinary risk factors in patients with at least six months of follow-up. In patients with at least twelve months follow-up and excluding those with nephrocalcinosis, symptomatic renal colic rate, stone formation rate and urological intervention rate were evaluated by means of the same test.

**Results**- 835 nephrolithiasis and nephrocalcinosis patients (537 males, 298 females) were evaluated at baseline. In 355 patients, effect of combined preventive measures on urinary risk factors was evaluated. Combined preventive measures significantly reduced median sodium excretion (*P*<0.05), calciuria (*P*<0.0001), uricosuria (*P*<0.0001) and phosphaturia (*P*<0.005) and significantly increased median urinary volume (*P*<0.0001). In patients with hyperoxaluria, increased protein intake, hypocitraturia and low urinary pH at baseline evaluation, combined preventive measures significantly reduced median oxalate excretion (*P*<0.0001) and protein intake (*P*<0.0001) and significantly increased median citrate excretion (*P*<0.0001) and urinary pH (*P*<0.0001), respectively. Combined preventive measures significantly reduced median symptomatic renal colic rate in 257 patients (*P*<0.0001), and median urological intervention rate in 254 patients (*P*<0.0001). The effect of preventive measures on the stone formation rate did not attain statistical significance.

**Conclusions**- Combined preventive measures have a significant effect on urinary risk factors. Additionally, it leads to a significant decrease in symptomatic renal colic rate and urological intervention rate. These are clinically relevant results for patients and are likely to cause a decrease in nephrolithiasis-related complications and health care costs.

**Keywords**- nephrolithiasis; prevention; recurrence;

# ABBREVIATIONS

ADPKD Autosomal Dominant Polycystic Kidney Disease

AHT Arterial Hypertension

AMI Acute Myocardial Infarction

BMI Body Mass Index

BPH Benign Prostatic Hypertrophy

CABG Coronary Artery Bypass Graft surgery

CAD Coronary Artery Disease

CKD Chronic Kidney Disease

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

CT Computed Tomography

CV Cardiovascular

eGFR Estimated Glomerular Filtration Rate

ESWL Extracorporeal shock wave lithotripsy

HIV Human Immunodeficiency Virus

IBD Inflammatory Bowel Disease

ICH GCP International Conference on Harmonisation Good Clinical Practice

IQR Interquartile range

MDRD Modification of Diet in Renal Disease

MSK Medullary Sponge Kidney

NaCl Sodium Chloride

NC Nephrocalcinosis

NHANES Health and Nutrition Examination Survey

NL Nephrolithiasis

OSAS Obstructive Sleep Apnea Syndrome

PAD Peripheral Artery Disease

PNL Percutaneous nephrolithotomy

PTCA Percutaneous Transluminal Coronary Angioplasty

PUJ stenosis Pelviureteric Junction stenosis

RF Risk factor

SD Standard deviation

TURP Transurethral Resection of the Prostate

URS Ureteroscopy

UTIs Urinary Tract Infections

# INTRODUCTION

Nephrolithiasis is a highly prevalent condition. Recent analysis estimates the prevalence at 10.6% in males and 7.1% in females in the United States (1). Lower prevalence rates have been reported in Europe (5-9%) and in Asia (1-5% )(2). In contrast, kidney stones are believed to be more common in Middle Eastern countries. Ahmad et al. retrospectively investigated the records of 5371 patients visiting a polyclinic in Saudi-Arabia and concluded that 19.1% of the patients were diagnosed with nephrolithiasis (3). Robertson et al. reported a higher lifetime stone expectancy in men in Saudi-Arabia compared to other countries such as the United States (20.1% vs 13.0%) (4). The geographic discrepancy is tentatively explained by differences in climate, lifestyle and dietary practices.

Prevalence rates have been increasing over the last several decades. The dataset of NHANES showed that the prevalence of symptomatic nephrolithiasis in the general population in the United States has increased from 3.2% in 1976-1980 to 5.2% in 1988-1994 and even to 8.4% in 2007-2010 (1,5). As the NHANES data are based on self-reported diagnosis of nephrolithiasis, asymptomatic kidney stones are missed in the analysis so that the true prevalence is presumably higher. In fact, according to a cohort study conducted by Boyce et al., 7.8% of the 5.047 asymptomatic adults that underwent a non-contrast-enhanced CT scan, appeared to have asymptomatic nephrolithiasis with an average of two stones of 3 mm per individual. During the following 10 year follow-up, 20.5% of them developed symptomatic episodes (6).

Nephrolithiasis is a highly recurrent disease. Daudon et al. demonstrated an overall recurrence rate of 42.7% and demonstrated that the frequency of stone recurrence varies with stone composition. Cystine stone formers have a high recurrence rate at 89.0% and also uric acid stone formers frequently develop new stones after a first stone, with recurrence rates of 50.9% and 51.6% for uric acid anhydrous and uric acid dihydrate stone formers respectively (7).

Stone recurrence strongly contributes to the morbidity and healthcare costs related to nephrolithiasis. A retrospective analysis of the use of healthcare resources by Pearl et al. (8) aimed to quantify the economic burden of nephrolithiasis in the United States. The authors found emergency room visits, hospitalizations, medical imaging, urological interventions and follow-up consultations to be the main direct costs. Indirect costs mainly involved hours of work lost; 30.0% had to take a leave of absence with an average of 19 hours of work lost. Despite the fact that hospitalization rates and length of stay declined, the annual total costs of patients with a primary diagnosis of nephrolithiasis appears to be increasing, which might be explained by the increasing prevalence.

In 2000, the cumulative costs in the United States for the medical care of nephrolithiasis patients were estimated at $2.1 billion dollars (9). Recent analysis predicts an annual increase in these costs by $1.2 billion dollars by 2030 (9), explained by the rising prevalence of nephrolithiasis and its risk factors such as metabolic syndrome, obesity and diabetes, which are all independently associated with stone formation (10-12).

It should be noted that nephrolithiasis is not a purely urologic condition, but is associated with several other diseases and should be regarded as a systemic disease. One of the best studied associations is the one with diabetes mellitus type 2 and metabolic syndrome (10-12). This is explained by insulin resistance, which alters the function of kidney tubule and results in lower ammonium excretion. Insulin resistance namely inhibits the Na+/H+ exchanger in the proximal tubule, which regulates proximal tubular NH4+ secretion and hence ultimately lowers the urinary pH, which is a risk factor for the development of uric acid kidney stones (13). Other associations include osteoporosis (14), gout (13,15), obstructive sleep apnea (16) and arterial hypertension (17). Furthermore, an increased risk for the development of CKD and ESRD is demonstrated (18) in kidney stone formers. This risk seems to depend on the number of kidney stones, as Dhondup et al. reported an increased risk for ESRD in recurrent stone formers as compared to incident stone formers (19).

Nephrolithiasis are not only associated with a number of risk factors for cardiovascular disease, they are also associated with an increased risk of cardiovascular events, including AMI, CAD ,CABG, PTCA, PAD and ischemic stroke (20-23).

Given the reduced quality of life of symptomatic stone formers (24) and the association with other diseases, it can be concluded that nephrolithiasis is both a frequent and severe disease. It is therefore important to develop efficient preventive measures capable to reduce both the recurrence rate and associated health care burden of nephrolithiasis, and to screen for associated diseases. This requires to understand the pathophysiological processes underlying stone formation in individual patients. All kidney stone formers should therefore receive a basic evaluation comprising medical history and physical examination, blood and urinalysis and diagnostic imaging. All kidney stones should also be examined by means of X-ray diffraction or infrared spectrophotometry, which is considered the gold standard (25).

According to the European Association of Urology guidelines, patients with nephrolithiasis should be advised to follow general preventive measures regarding their fluid and dietary intake, which are summarized in table 1. Depending on the results of the metabolic evaluations, other specific preventive measures, which can be found in table 2, should be considered (25).

Table 1 – general preventive measures

|  |
| --- |
| General preventive measures |
| Fluid intake (25) | Increase diuresis to 2.0-2.5 L/day (neutral pH beverages, circadian drinking) (25) for goal specific weight of urine < 1.0Balancing of excess fluid loss  |
| Nutritional advice ( 26-29) | Balanced diet with normal calcium content (1.0-1.2g/day, limited NaCl content (4.0-5.0 g/day) (26) and limited animal protein content (0.8-1.0 g/kg per day) (29), rich in vegetables and fibersFructose intake reduction |
| Lifestyle advice (28, 30) | Target BMI 25.0-28.0 kg/m² (adults)Adequate physical activity  |

Table 2 – specific preventive measures

|  |
| --- |
| Specific preventive measures  |
| Stone analysis  | Suggested preventive measures  |
| Calcium oxalate stones (whewellite/weddellite) | General preventive measures + low oxalate dietCalcium supplements with meals if persistent hyperoxaluria despite dietary modificationsThiazide or thiazide-like agents if persistent hypercalciuria despite dietary modifications (31-34)Alkalinizing agents if persistent hypercalciuria or hypocitraturia (35-37)Allopurinol if hyperuricosuria and hyperuricemia (38)Magnesium if hypomagnesuria  |
| Calcium phosphate stones  | General preventive measures Thiazide or thiazide-like agents if persistent hypercalciuria despite dietary modifications (31-34)Urinary acidification if inadequately high urine pH Antibiotics if urinary tract infection  |
| Uric acid stones  | General preventive measures Purine intake reduction and allopurinol if persistent hyperuricosuria (38)Alkalinizing agents if inadequate urine pH (target pH 6.2-6.8 for prevention, 6.5-7.2 for chemolysis) (39) |
| Ammonium urate stones  | General preventive measures Antibiotics if urinary tract infectionUrinary acidification if inadequately high urine pH |
| Struvite and infection stones  | General preventive measures Complete surgical stone removal Short- or long-term antibiotic treatment Acidification if inadequate urine pH Urease inhibition if presence of urease-producing germs  |
| Cystine stones  | High fluid intake > 3.0L/day + low methionine diet Alkalinizing agents if inadequate urine pH (target pH: 7.5-8.0) (35,40)Tiopronin for complex formation with cystine if other measures are insufficient or patients with cystine excretion >3.0 mmol/day (40) |

A prospective randomised study by Borghi et al. (26) examined the influence of increased urinary output as a preventive measure. The authors demonstrated a significant decrease in recurrent stone formation in idiopathic calcium stone formers by increasing the diuresis to ≥2.0 L/day (27). This was later confirmed by another randomized controlled trial (42) that evaluated the effect of verapamil and high fluid intake on stone recurrence rates after ESWL. Increasing fluid intake was proven more effective than treatment with calcium channel blockade and compared to controls. To this day, increased urinary output remains the most important dietary preventive measure.

With the aim of lowering the recurrence of nephrolithiasis in patients with idiopathic hypercalciuria, in the past a low dietary calcium intake was thought to be a possible preventive strategy. To address this question a randomized trial comparing 60 patients following a low calcium diet (10 mmol per day) and 60 patients following a normal calcium diet (30 mmol per day) with reduced animal protein (21g per day) and salt intake (50 mmol per day) was conducted by Borghi et al. After five years, 23 patients of the low calcium group had relapsed as compared to only 12 patients of the normal calcium group, which was a statistically significant difference. The urinary excretion of oxalate was also decreased in the second group. This led to the conclusion that a normal dietary calcium intake combined with a lowered intake of salt and animal protein is a better preventive strategy in this indication and disproved the theory that reduced calcium intake would prevent against kidney stone recurrence (30).

Ettinger et al. analysed the efficiency of potassium-magnesium citrate in patients with recurrent calcium oxalate nephrolithiasis. At three year-follow up the authors demonstrated that a potassium-magnesium citrate treatment led to significantly fewer relapses compared to placebo (12.9% vs 63.6%) (38). Another important insight was obtained by the reports of Borghi et al. (33), Laerum et al. (35) and Ohkawa et al. (34), by demonstrating that the use of thiazide or thiazide-like agents lowers the calciuria in idiopathic hypercalciuria and can be used as a prophylaxis for prevention of recurrent calcium oxalate or phosphate stones.

The efficacy of allopurinol for the prevention of recurrent calcium oxalate stone formation in patients with hyperuricosuria was demonstrated by comparing the number of symptomatic events after allopurinol therapy or placebo therapy. The allopurinol group was found to have a significantly lower amount of symptomatic events and longer interval until the first relapse (39).

As mentioned before, several randomized controlled trials demonstrated the effect of an increased fluid intake (26), dietary measures (30) and medical therapy (32-39) on the stone formation and growth rate of idiopathic calcium nephrolithiasis. While these studies evaluated the effect of one measure in the strict setting of a randomized, controlled trial, only few studies have evaluated the effect of combined measures in routine real-life practice. Hosking et al. showed that recommending the combination of increased fluid intake and dietary measures is an important and effective preventive measure in patients with idiopathic calcium nephrolithiasis (43). In total 108 patients were advised to increase fluid intake to more than two and a half litres per day and apply dietary measures, including less meat intake in patients with hyperuricosuria at baseline and less calcium intake in patients with hypercalciuria. After five years of follow-up, there was no evidence of new stone formation in 63 patients (58.3%). Iguchi and associates (44) concluded that individually adjusted dietary measures in calcium nephrolithiasis can lead to a significant decrease in four-year recurrence rates compared to general dietary measures even after ceasing the ambulant follow-up (27.4% vs 67.5%). Also in patients treated with medication, addition of individually adjusted dietary measures led to significantly lower recurrence rates.

Preventive measures, were also proven useful after urological surgery (45,46). A study by Kang et al. (45) revealed that instituting individualized interventions, including high fluid intake combined with dietary measures and medical therapy if needed, could benefit patients who have undergone PNL. A significant decrease was observed in the stone formation rates of patients who had received individual medical therapy compared to those who did not (0.7 vs 0.0 stones per patients per year). A significantly higher proportion of patients went into remission after instituting individual medical therapy, this was true both for patients with (77.0% vs 21.0%) and without (87.0% vs 29.0%) residual fragments after PNL. The same conclusion on stone formation rates could be drawn for patients who had undergone ESWL (46). Fine et al. demonstrated a significant larger decrease in stone formation rates in patients who received medical therapy after ESWL compared to those who did not. This was true both for patients with (2.5 to 0.0 vs 1.3 to 0.8 stones per patient per year) and without (0.7 to 0.0 vs 0.8 to 0.4 stones per patient per year) residual stone fragments after ESWL.

Finally, Parks and Coe concluded in their retrospective analysis of their large kidney stone patients cohort in Chicago (47) that adequate metabolic evaluation, follow-up consultations and treatment including dietary measures and additional medical treatment when needed, did indeed lower the recurrence rate of stone formation, stone-related interventions and improved urinary risk factors in 24-hours urine analysis. They also reported that these improvements was durable and could be documented for more than 20 years of follow-up (47). However, the biggest obstacle proved to be motivating patients to stay in follow-up and carry out the 24-hour urine collection. Parks and Coe noted an annual loss of follow-up of 20.0-38.0% of patients (48). Since to our knowledge there are few other studies confirming these results nor providing other insights, acquiring more data on prospectively followed patient cohorts is necessary.

Nephrocalcinosis is a condition that indicates the presence of calcium oxalate or calcium phosphate depositions in the kidneys. It is frequently associated with nephrolithiasis (49). The depositions are mostly found in the renal medulla, termed medullary nephrocalcinosis, but less often they can also be found in the cortex (50). In adults, the leading causes of medullary nephrocalcinosis are medullary sponge kidney, hyperparathyroidism and distal renal tubular acidosis (51). Also in these patients, preventive measures to reduce additional calcium oxalate or calcium phosphate deposition, is recommended.

At the Kidney stone prevention clinic of the UZ Brussel, patients with nephrolithiasis and nephrocalcinosis are treated with preventive measures guided by repeated metabolic evaluation in order to improve the metabolic kidney stone formation risk factors and to decrease renal colic episodes, number of urological interventions, new stone formation and growth of residual stones.

In this retrospective survey, we evaluate if these preventive measures effectively result in these goals and address the following research questions

1. To what extent do preventive measures influence urinary risk factors involved in stone ok recurrence?

2. To what extent do preventive measures influence stone formation rates in patients with nephrolithiasis? As nephrocalcinosis progression is difficult to quantify, this research question will only be addressed to nephrolithiasis patients, excluding those with nephrocalcinosis.

3. To what extent do preventive measures influence the symptomatic renal colic rate in patients with nephrolithiasis, excluding patients with nephrocalcinosis? As patients with nephrocalcinosis only develop renal colic when associated with nephrolithiasis, this research question will exclude patients with nephrocalcinosis.

4. To what extent do preventive measures influence the number of urological interventions aa compared to the period before the preventive measures were imposed? This research question will exclude patients with nephrocalcinosis given calcium oxalate and calcium phosphate depositions cannot be removed by means of urological procedures.

This results in the following study objectives:

* Primary objectives
	+ To investigate whether the imposed preventive measures improve the urinary risk factors for kidney stone formation in patients with nephrolithiasis and nephrocalcinosis.
	+ To investigate whether the imposed preventive measures result in a reduction of symptomatic renal colic episode rate in patients with nephrolithiasis.
* Secondary objectives
	+ To investigate whether the imposed preventive measures improve the urinary risk factors for kidney stone formation in those patients with nephrolithiasis and nephrocalcinosis who present urinary risk factors at baseline metabolic evaluation.
	+ To investigate whether the imposed preventive measures result in a reduction of kidney stone formation rate in patients with nephrolithiasis.
	+ To investigate whether the imposed preventive measures result in a reduction of urological intervention rate in patients with nephrolithiasis.

# PATIENTS AND METHODS

## OVERALL STUDY DESIGN

This is a retrospective cohort analysis including all nephrolithiasis and nephrocalcinosis patients that consulted at the Kidney stone prevention clinic at the Universitair Ziekenhuis Brussel between 22/12/2004 and 31/12/2020. Patients who did not attend follow-up for more than 36 months after the last visit were not included in the analysis. In patients resuming follow-up, after loss to follow-up during more than 36 months, the longest follow-up period was taken into account.

## TREATMENT PROTOCOL OF THE KIDNEY STONE PREVENTION CLINIC

At the Kidney stone prevention clinic patients were treated according to and guided by the results of kidney stone analysis and repeated metabolic evaluation.

When consulting the kidney stone prevention clinic, an in-depth anamnesis took place, during which the patient's eating and drinking habits, medical and surgical history, family history and medication use were examined. In addition, a physical examination was carried out and, if the patient had brought along stone fragments, these were sent for analysis by means of infrared spectrophotometry.

Prior to the baseline consultation, patients should also have had recent medical imaging, a blood analysis, a 24-hour urine collection and a microscopic urinalysis. If these were not yet completed before the first consultation, these examinations were requested. Only when the results of these investigations were known, preventive measures could be initiated. A complete baseline evaluation was also the prerequisite for this consultation to be considered as baseline evaluation for the present analysis.

During their follow-up at the Kidney stone prevention clinic, all patients were recommended to increase their oral fluid intake for a minimum urinary output > 2000.0 ml/24 hours, except for patients with cystinuria and patients with enteric or primary hyperoxaluria to whom a minimum urinary output of 3000.0 ml/24 hours was recommended. In all patients, reduced sodium intake was recommended (goal < 150.0 mmol/24 hours, < 100.0 mmol/24 hours in cystinuria patients). Normal protein intake (goal < 1.0 g/kg ideal weight/24 hours) and normal calcium intake (800.0-1000.0 mg/24 hours) was recommended to all patients. Patients with hyperoxaluria were additionally treated with an oxalate-restricted diet and calcium supplements with meals in case of insufficient metabolic control. In patients with persisting hypercalciuria, thiazide or thiazide-like diuretics were additionally prescribed. Patients with uric acid nephrolithiasis received treatment by a purine-restricted diet, urinary alkalinization by means of potassium citrate, sodium citrate or sodium bicarbonate (for goal pH 6.0-6.5 in case of no residual stones, goal 6.5-7.0 in case of residual stones) and addition of allopurinol or febuxostat if there was insufficient metabolic control. Urinary alkalinization by means of potassium citrate, sodium citrate or sodium bicarbonate was also used in patients with hypocitraturia or persistent positive crystalluria. Cystinuria patients were treated with a methionine-restricted diet, urinary alkalinization by means of potassium citrate, sodium citrate or sodium bicarbonate (for goal pH 7.5-8.0) and exceptionally by thiol-binding agents in case of insufficient metabolic control. Primary hyperparathyroidism was treated by parathyroidectomy. Patients with distal renal tubular acidosis were treated by means of urinary alkalinization and thiazide or thiazide-like diuretics in case of hypercalciuria. Struvite stones were treated with long-term antibiotic treatment, urological removal of stones and urinary acidification.

## DATA RETRIEVAL

Data used for this analysis were retrieved from the Kidney stone prevention clinic database, approved by the Ethics committee of the UZ Brussel/VUB on 12/8/2019 (EC 2019-155). This Kidney stone prevention clinic database stores data collected from the patients followed at the Kidney stone prevention clinic as part of their normal clinical follow-up. No additional data were obtained for the purpose of this database nor for the purpose of this retrospective analysis.

The following data were obtained from the database:

**Baseline data** (data obtained at the first consultation at the Kidney stone prevention clinic):

* Date of birth, gender, ethnicity
* Height and weight
* Medical and surgical history
In particular the following comorbidities were evaluated:
	+ Hypertension, cardiovascular disease, CKD, diabetes, gout, dyslipidemia, obesity, OSAS, osteopenia/osteoporosis, renal/urological abnormalities, gastro-intestinal comorbidities, metabolic disorders, nephrocalcinosis, medullary sponge kidney, tetraparesis, Dent's disease.
		- Renal/urological abnormalities comprised prostatic disease, unique functioning kidney, ADPKD, horseshoe kidney, kidney duplication, PUJ stenosis, ureter stenosis, urethra stenosis, vesicourethral reflux, neurogenic bladder, cystectomy, congenital mega-ureter, bladder polyp/tumor and recurrent UTIs. Prostatic disease comprised TURP, total prostatectomy, BPH, prostatic carcinoma.
		- Gastro-intestinal comorbidities comprised IBD, ileal resection, colon resection, pancreatic insufficiency, bariatric surgery (sleeve gastrectomy, gastric bypass surgery and gastric banding), celiac disease and lactose intolerance.
		- Metabolic disorders comprised (normocalcemic) hyperparathyroidism, distal renal tubular acidosis (with/without presence of Sjögren's syndrome), hypercalcemia, enteric hyperoxaluria, cystinuria and Fanconi syndrome.
* Information regarding nephrolithiasis history: age at the time of the first renal colic episode, number of episodes and urological interventions since the first episode until the first consultation
* Infrared spectrophotometric stone analysis
* Results of medical imaging, more specifically number of residual stones
* Results of blood analysis: glucose, urea, eGFR (MDRD or CKD-EPI), uric acid, sodium, potassium, chloride, bicarbonate, anion gap, phosphorus, calcium, magnesium, 25-OH-vitamin D, intact parathyroid hormone
* Results of microscopic urine analysis
* Results of the 24-hour urine analysis
	+ 24-hours urinary volume, expressed in mL/24 hours
	+ 24-hour urinary oxalate excretion , expressed in mg/24 hours
	+ 24-hour urinary citrate excretion, expressed in µmol/24 hours
	+ 24-hour urinary calcium excretion, expressed in mmol/24 hours
	+ 24-hour urinary phosphorus excretion, expressed in mmol/24 hours
	+ 24-hour urinary uric acid excretion, expressed in mg/24 hours
	+ 24-hour urinary sodium excretion, expressed in mmol/24 hours
	+ 24-hour urinary urea excretion, expressed in g/24 hours
	+ 24-hour diuresis, expressed in mL/24 hours
	+ Urinary pH

**Follow-up data** (data obtained at the follow-up consultations at the Kidney stone prevention clinic):

* Date of consultation
* Results of microscopic urine analysis
* Results of the 24-hour urine analysis
	+ 24-hours urinary volume, expressed in mL/24 hours
	+ 24-hour urinary oxalate excretion, expressed in mg/24 hours
	+ 24-hour urinary citrate excretion, expressed in µmol/24 hours
	+ 24-hour urinary calcium excretion, expressed in mmol/24 hours
	+ 24-hour urinary phosphorus excretion, expressed in mmol/24 hours
	+ 24-hour urinary uric acid excretion, expressed in mg/24 hours
	+ 24-hour urinary sodium excretion, expressed in mmol/24 hours
	+ 24-hour urinary urea excretion, expressed in g/24 hours
	+ Urinary pH
* Number of symptomatic renal colic episodes since the last consultation
* Type and number of urological interventions since the last consultation
* Number of spontaneously eliminated urinary stones since the last consultation
* Results of medical imaging, if performed, more specifically new observed stone formation or stone growth
* Imposed preventive measures (dietary measures, increasing urinary volume alkalinizing therapy (potassium-citrate, sodium citrate, sodium bicarbonate supplements…), calcium supplements, allopurinol or febuxostat, thiazide or thiazide-like diuretic and thiol-binding agents tiopronin or D-penicillamine.

## EVALUATION OF URINARY RISK FACTORS

Of all patients with nephrolithiasis and nephrocalcinosis followed at the Kidney stone prevention clinic, mean and median urinary oxalate, calcium, phosphorus, uric acid, sodium and citrate excretion were calculated as well as the mean and median urinary pH, urinary volume and protein intake at baseline evaluation.

The number of patients with urinary risk factors was calculated; these were defined as follows:

* Hyperoxaluria was defined as urinary oxalate excretion > 45.0 mg/24 hours
* Hypercalciuria was defined as urinary calcium excretion ≥0.1 mmol/kg ideal weight /24 hours
* Increased urinary phosphorus excretion was defined as urinary phosphorus excretion > 42.0 mmol/24 hours
* Increased urinary uric acid excretion was defined as urinary uric acid excretion > 750.0 mg/24 hours in females and >800.0 mg/24 hours in males
* Increased sodium excretion was defined as urinary sodium excretion > 150.0 mmol/24 hours
* Increased protein intake was defined as protein intake > 1.0 g/kg ideal weight/24 hours
* Low urinary output was defined as urinary volume < 2000.0 ml/24 hours
* Hypocitraturia was defined as urinary citrate excretion ≤ 1500.0 µmol/24 hours
* Low urinary pH was defined as urinary pH < 5.5

In all patients with nephrolithiasis and nephrocalcinosis with at least six months clinical and biochemical follow-up mean and median urinary oxalate, calcium, phosphorus, uric acid, sodium and citrate excretion were calculated as well as the mean and median urinary pH, urinary volume and protein intake at last clinical and biochemical follow-up.

## DETERMINATION OF THE PRE- AND POSTTREATMENT RATES

### Nephrolithiasis and nephrocalcinosis diagnosis

NL/NC diagnosis was defined as the first symptomatic renal colic episode or first asymptomatic visualization of nephrolithiasis on medical imaging.

### Symptomatic renal colic rate

A symptomatic renal colic was defined as a typical acute loin to groin colicky pain associated with nausea, vomiting and renal angle tenderness, with or without microscopic or macroscopic haematuria and with or without medical imaging confirmation. Any symptomatic renal colic occurring within 30 days of a prior symptomatic renal colic was regarded as one single renal colic.

In all patients with nephrolithiasis and excluding those with nephrocalcinosis, pre-treatment symptomatic renal colic rate was calculated. The rate was calculated as the number of symptomatic renal colic episodes since the diagnosis of nephrolithiasis, divided by the number of years between the diagnosis and first consultation at the Kidney stone prevention clinic. If insufficient data were available, the pre-treatment symptomatic renal colic rate was calculated based on the number of symptomatic renal colics during the five years before the first consultation at the Kidney stone prevention clinic.

In all patients with nephrolithiasis with minimum 12 months clinical and biochemical follow-up, excluding those with nephrocalcinosis, post-treatment symptomatic renal rate was calculated. The rate was calculated as the number of symptomatic renal colic episodes since the first consultation at the kidney stone prevention clinic until final follow-up divided by the number of years in follow-up.

### Kidney stone formation rate

In all patients with nephrolithiasis and excluding those with nephrocalcinosis, pre-treatment stone formation rate was calculated. The rate was calculated as the number of kidney stones formed since the diagnosis of nephrolithiasis, divided by the number of years between the diagnosis and the first consultation at the Kidney stone prevention clinic. This equals the number of kidney stones removed by urological interventions or spontaneous elimination and the number of residual stones visualized on medical imaging (by means of ultrasound or CT-scan) at the start of preventive measures divided by the number of years between the diagnosis and the first consultation at the Kidney stone prevention clinic. If insufficient data were available to calculate kidney stone formation rate since diagnosis, the pre-treatment stone formation rate was calculated based on the number of kidney stones formed during the five years before the first consultation at the Kidney stone prevention clinic.

To account for the time period during which kidney stones are formed but remain asymptomatic, two additional calculations were made. In a first calculation, in patients with an interval between diagnosis of nephrolithiasis and first consultation at the Kidney stone prevention clinic less than five years, the time interval for formation of stones up to the date of first consultation at the Kidney stone prevention clinic was set at five years. In a second approach, the actual pre-treatment intervals were used but only patients with a pre-treatment interval longer than three years were taken into account.

In all patients with nephrolithiasis with minimum 12 months clinical, biochemical and imaging follow-up at the Kidney stone prevention clinic, excluding those with nephrocalcinosis and with, post-treatment formation rate was calculated. The rate was calculated as the number of spontaneously or urologically eliminated kidney stones not visible on medical imaging at the start of preventive measures plus number of new stones and number of grown stones visible on medical imaging (by means of ultrasound or CT-scan) since the first consultation at the Kidney stone prevention clinic until final medical imaging divided by the number of years with imaging follow-up. If both ultrasound and CT had been performed, only the CT scan was considered.

### Urological intervention rate

In all patients with nephrolithiasis and excluding those with nephrocalcinosis, pre-treatment urological intervention rate was calculated. The rate was calculated as number of urological procedures performed for the indication of nephrolithiasis since the diagnosis of nephrolithiasis until the first consultation at the Kidney stone prevention clinic divided by the number of years between the diagnosis and the first consultation at the Kidney stone prevention clinic. If insufficient data were available, the pre-treatment urological intervention rate was calculated based on the number of urological interventions during the five years before the first consultation at the Kidney stone prevention clinic.

Urological interventions included extracorporeal shockwave lithotripsy, ureterorenoscopy, double-J stenting, (mini-) percutaneous nephrolithotomy, bladder stone lithotripsy and (partial) nephrectomy.

If a double J stent was placed prior to ESWL, URS, PNL or spontaneous elimination, this was always considered a separate procedure. A bilateral URS was noted as carrying out two URS.

In all patients with nephrolithiasis with minimum 12 months clinical and biochemical follow-up at the Kidney stone prevention clinic, excluding those with nephrocalcinosis, post-treatment urological intervention rate was calculated. The rate was calculated as number of urological procedures performed for the indication of nephrolithiasis since the first consultation at the Kidney stone prevention clinic until final follow-up divided by the number of years in follow-up.

## DEFINITIONS

### Terms and definitions

|  |  |
| --- | --- |
| Age of NL/NC diagnosis | Age at the first symptomatic renal colic episode or first asymptomatic visualization of nephrolithiasis on medical imaging |
| Arterial hypertension | Systolic blood pressure values ≥ 140.0 mmHg and/or diastolic blood pressure values ≥90.0 mmHg, or treated with antihypertensive medication |
| Bariatric surgery | Including sleeve gastrectomy, gastric bypass and gastric banding |
| Cardiovascular disease | Including AMI, CAD, CABG, PAD, PTCA and ischemic stroke |
| CKD | eGFR (MDRD or CKD-EPI) <60.0 mL/min for minimum three months |
| Diabetes | Including diabetes type 1, type 2 and unclassified diabetes |
| Gastro-intestinal comorbidities | Including IBD, ileal resection, colon resection, pancreatic insufficiency, bariatric surgery (sleeve gastrectomy, gastric bypass and gastric banding), celiac disease and lactose intolerance |
| IBD | Including Crohn's disease and ulcerative colitis |
| Metabolic disorders | Including (normocalcemic) hyperparathyroidism, distal renal tubular acidosis (and presence of Sjögren's syndrome), hypercalcemia, enteric hyperoxaluria, cystinuria and Fanconi syndrome |
| Obesity | BMI ≥ 30.0 kg/m² |
| Prostatic disease | Including prostate carcinoma, TURP, BPH and prostatectomy |
| Renal and urological abnormalities | Including prostatic disease, unique functioning kidney, ADPKD, horseshoe kidney, kidney duplication, PUJ stenosis, ureter stenosis, urethra stenosis, vesicourethral reflux, neurogenic bladder, cystectomy, congenital mega-ureter, bladder polyp/tumor and recurrent UTIs |
| Unique functioning kidney | Including nephrectomy, kidney atrophy and congenital unique kidney |

### Stone compositions

The stone compositions were determined by means morphoconstitutional stone analysis, comprising optic microscopy and Fourier-transform infrared spectrophotometry, which is considered the gold standard (23). Hereafter they were categorised according to the definitions of the European Renal Stone Network Survey, which can be found in attachment 1. Thus, seven categories were created:

* **Calcium oxalate stones**: >50.0% of the dry weight of the stone represented by calcium oxalate
* **Calcium phosphate stones**: >50.0% of the dry weight of the stone represented by calcium phosphate
* **Brushite stones**: any brushite in the stone
* **Uric acid stones**: >50.0% of the dry weight of the stone represented by uric acid
* **Struvite stones**: any struvite in the stone
* **Cystine stones**: any cystine in the stone
* **Mixed stones**: stones that did not meet any of the previous definitions

## STATISTICAL ANALYSIS

### Baseline characteristics of the study population

Baseline properties of the population were reported in terms of descriptive statistics using mean ± SD for normally distributed continuous variables, median with inter-quartile range (IQR) for continuous variables without normal distribution and proportions for categorical variables.

### Evaluation of the mean reduction in urinary risk factors

The effect of preventive measures on urinary risk factors for stone formation was investigated on an intention-to-treat basis by analysing results of the 24-hour urine analysis data collected at baseline and follow-up visits after initiating preventive measures.

The Wilcoxon signed-rank test was used to compare the urinary risk factors pre- and post-treatment in all patients with nephrolithiasis and nephrocalcinosis with at least six months clinical and biochemical follow-up at the kidney stone prevention clinic.

### Evaluation of the mean reduction in pre- to posttreatment rates

The effect of preventive measures on the symptomatic renal colic rate, the kidney stone formation rates and urological intervention rates were investigated on an intention-to-treat basis by analyzing clinical and imaging data collected during baseline and follow-up consultations at the kidney stone prevention clinic.

The Wilcoxon signed-rank test was used to compare the mean pre- and post-treatment in all patients with nephrolithiasis (but excluding those with nephrocalcinosis) with at least 12 months clinical, biochemical (and imaging follow-up in the kidney stone formation rate) at the Kidney stone prevention clinic.

## ETHICS

An ICH GCP training certificate was obtained before starting this study and can be found in attachment 2. The protocol for the present study was reviewed and approved by the Ethics committee on 3/2/2021 (EC 2021-012). Earlier, the Kidney stone prevention clinic database obtained approval on 12/8/2019 (EC 2019-155). Both approvals can be found in attachment 3.

# RESULTS

## BASELINE CHARACTERISTICS OF THE STUDY POPULATION

### Patient demographics

The baseline characteristics of the study population are shown in table 3. In total 835 patients were included in the analysis, of whom 298 women and 537 men. This corresponds to a male to female ratio of 1.8 to 1.0.

The majority of the patients were Caucasian (600 patients; 382 males, 218 females), followed by Middle-East and North-African ethnicity (204 patients; 138 males, 66 females).

The mean BMI of the entire study population was 26.7±4.9 kg/m² , when subdivided by sex the mean BMI was 27.2±4.6 kg/m² for men and 25.7±5.3 kg/m² for women. In total, 24.4% of the study population was obese.

The median age at diagnosis of nephrolithiasis/nephrocalcinosis for the entire study population was 36.0 years (25.0-49.0). The mean age at first consultation at the kidney stone prevention clinic was 47.0 years (35.0-58.0). This results in a median time interval of 3.7 years (0.4-12.1) between the diagnosis of nephrolithiasis/nephrocalcinosis and the first consultation at the kidney stone prevention clinic for the entire study population.

Table 3: patient demographics

|  |  |  |  |
| --- | --- | --- | --- |
|  | Total (n = 835) | Male(n = 537) | Female(n = 298) |
| **Baseline characteristics**  |
| BMI (kg/m²), mean±SD | 26.7±4.9 | 27.2±4.6 | 25.7±5.3 |
| Age at NL/NC diagnosis (yr), median (IQR) | 36.0 (25.0-49.0) | 36.0 (25.0-49.0) | 36.0 (25.8-51.0) |
| Age at first consultation (yr), median (IQR) | 47.0 (35.0-58.0) | 47.0 (36.0-57.0) | 47.0 (35.0-58.0) |
| Interval between NL/NC diagnosis and first consultation (yr), median (IQR) | 3.7 (0.4-12.1) | 4.7 (0.5-13.1) | 0.1 (0.4-10.5) |
| **Ethnicities**  |
| Caucasian  | 600 | 382 | 218 |
| Middle-East and North-African  | 204 | 138 | 66 |
| Hispanic | 14 | 8 | 6 |
| Black | 9 | 5 | 4 |
| Asian  | 8 | 5 | 3 |

### Stone compositions

In 482 patients (57.7%), the stone composition, examined by morphoconstitutional analysis including Fourier-transform infrared spectroscopy, was known. Of these, 73.9% were calcium oxalate stones, 7.7% uric acid stones, 4.4% cystine stones, 3.9% mixed stones , 2.9% calcium phosphate stones, 2.3% struvite stones and 2.1% brushite stones.

Table 4 demonstrates the distribution of stone compositions in the entire study population and categorized by ethnicity. Overall, calcium oxalate stones were the most common stones in all ethnicities, except for the Black population where the only kidney stone with known composition was uric acid.

Table 4: stone compositions in patients with known stone composition

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Etnicity | Calcium oxalate stones | Uric acid stones | Cystine stones | Mixed stones  | Calcium phosphate stones | Struvite stones | Brushite stones |
| Total study population (n = 482) | 370(73.9%) | 37(7.7%) | 21(4.4%) | 19(3.9%) | 14(2.9%) | 11(2.3%) | 10(2.1%) |
| Caucasian (n = 349) | 259(74.2%) | 31(8.9%) | 16(4.6%) | 14(4.0%) | 12(3.4%) | 9(2.6%) | 8(2.3%) |
| Middle-East and North-African (n = 119) | 101(84.8%) | 4(3.4%) | 4(3.4%) | 5(4.2%) | 2(1.7%) | 1(0.8%) | 2(1.7%) |
| Hispanic (n = 8) | 7(87.5%) | 0 | 0 | 0 | 0 | 1(12.5%) | 0 |
| Asian (n = 5) | 3(60.0%) | 1(20.0%) | 1(20.0%) | 0 | 0 | 0 | 0 |
| Black (n = 1)  | 0 | 1(100.0%) | 0 | 0 | 0 | 0 | 0 |

### Relevant comorbidities

Table 5 lists the relevant comorbidities within our entire study population as well as in the subpopulations per stone type. In total, 35.0% of the study population had no known relevant comorbidities.

Our study population of stone-formers had a high prevalence of cardiovascular risk factors, with 28.0% suffering from AHT, 24.3% from obesity, 22.5% from dyslipidaemia, 14.3% from diabetes (13.4% diabetes type 2, 0.6% type 1, 0.2% unclassified diabetes) , 4.3% from OSAS and 3.7% from gout. Furthermore, 7.1% suffered from cardiovascular disease and 13.3% from chronic kidney disease. The mean serum creatinine and eGFR (MDRD or CKD-EPI) in patients with CKD were 1.4 mg/dL and 49.0 mL/min, respectively.

Renal and urological abnormalities were found in 15.1%, with most commonly prostatic disease in 3.6%, and recurrent UTIs in 5.5%. Gastro-intestinal comorbidities were reported in 7.3% of the patients, including IBD in 2.4%, ileal resection in 1.8%, pancreatic insufficiency in 0.4%, and gastric bypass surgery in 1.1%. The reported prevalence of osteopenia and osteoporosis was 11.7%. Metabolic disorders were found in 12.8% of the patients, with (normocalcemic) hyperparathyroidism in 5.0%, enteric hyperoxaluria in 3.8%, distal tubular acidosis in 0.7% and cystinuria in 3.1%. As already mentioned, nephrocalcinosis was present in 3.6% and medullary sponge kidney in 2.0%.

Table 5: relevant comorbidities

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total study population(n=835) | Calcium oxalate stones(n=370) | Uric acid stones(n=37) | Cystine stone(n = 21) | Mixed stones (n = 19) | Calcium phosphate stones(n=14) | Struvite stones(n=11) | Brushite stones(n=10) |
| AHT | 234 (28.0%) | 106 (28.7%) | 11 (29.7%) | 5 (23.8%)  | 5 (26.3%) | 5 (35.7%) | 1 (9.1%)  | 3 (30.0%) |
| Obesity | 204 (24.4%) | 91 (24.6%) | 11 (29.7%) | 7 (33.3%)  | 8 (42.1%)  | 6 (42.8%) | 2 (18.2%)  | 2 (20.0%) |
| Dyslipidemia | 188(22.5%) | 77 (20.8%) | 12 (32.4%) | 6 (28.6%) | 2 (10.5%) | 0  | 1 (9.1%)  | 3 (30.0%)  |
| Diabetes* Type 1
* Type 2
* Unclassified
 | 119 (14.3%)5 (0.6%)112 (13.4%)2 (0.2%) | 58 (15.7%)1 (0.3%)55 (14.9%)2 (0.5%) | 5 (13.5%)05 (13.5%)0 | 3 (14.3%)03 (14.3%)0  | 3 (15.8%)03 (15.8%)0  | 1 (7.1%)01(7.1%)0 | 1 (9.1%) 01 (9.1%) 0 | 2 (20.0%)02 (20.0%)0 |
| CV disease | 59 (7.1%) | 22 (6.0%) | 3 (8.1%)  | 2 (9.5%)  | 2 (10.5%)  | 1 (7.1%)  | 0  | 1 (10.0%) |
| Gout | 31 (3.7%) | 12 (3.2%) | 1 (2.7%) | 0  | 0  | 1 (7.1%)  | 0  | 1 (10.0%) |
| OSAS | 36 (4.3%) | 11 (3.0%) | 1 (2.7%)  | 1 (4.8%) | 1 (5.3%) | 1 (7.1%)  | 0  | 0  |
| CKD | 111 (13.3%) | 42 (11.4%) | 4 (10.8%) | 4 (19.1%)  | 1 (5.3%)  | 2 (14.3%) | 0  | 0  |
| Urologic and renal abnormalities* Prostatic disease
* Unique functioning kidney
* ADPKD
* Recurrent UTIs
 | 126 (15.1%)30 (3.6%)13 (1.6%)1 (0.1%)46 (5.5%) | 44 (11.9%)16 (4.3%)6 (1.6%)013 (3.5%) | 4 (10.8%)2 (5.4%)01 (2.7%)0 | 6 (28.6%)1 (4.7%)2 (9.5%) 01 (4.8%)  | 4 (21.1%)01 (5.3%)02 (10.5%) | 3 (21.4%)0002 (14.3%) | 4 (36.4%)1 (9.1%)002 (18.2%) | 2 (20.0%)0000 |
| GI comorbidities* IBD
* Ileal resection
* Colon resection
* Pancreatic insufficiency
* Gastric bypass
 | 61 (7.3%)20 (2.4%)15 (1.8%)5 (0.6%)1 (0.1%)9 (1.1%) | 21 (5.7%)6 (1.6%)7 (1.9%)2 (0.5%) 1 (0.3%)4 (0.8%) | 3 (8.1%)2 (5.4%) 1 (2.7%)000 | 1 (4.8%)0 0000 | 1 (5.3%)1 (5.3%)0000 | 000000 | 1 (9.1%)1 (9.1%)0000 | 00000 0 |
| Osteopenia/ osteoporosis | 98 (11.7%) | 42(11.3%) | 4(10.8%)  | 4(19.1%)  | 3(15.8%) | 0 | 1(9.1%)  | 1(10.0%) |
| Metabolic disorders* Enteric hyperoxaluria
* Distal tubular acidosis
* Hyperparathyroidism
* Cystinuria
 | 107 (12.8%)32 (3.8%)6 (0.7%)42 (5.0%)26 (3.1%) | 45 (12.2%)17 (4.6%)2 (0.5%)15 (4.1%)11 (3.0%) | 3 (8.1%)1 (2.7%)002 (5.4%) | 1 (4.8%)1 (4.8%)000 | 4 (21.1%)004 (21.1%)0 | 1 (7.1%)0001 (7.1%) | 3 (27.3%)002 (18.2%)1 (9.1%)  | 3 (30.0%)003 (30.0%)0 |
| Nephrocalcinosis | 30 (3.6%) | 13 (3.5%)  | 0 | 1(4.8%)  | 0  | 0  | 0  | 0  |
| MSK | 17 (2.0%) | 9 (2.4%) | 0  | 0  | 0  | 0 | 0 | 0 |
| Dent’s disease | 1 (0.1%) | 0 | 0 | 0 | 0 | 0 | 1 (9.1%) | 0 |
| Radiotherapy small pelvis | 1 (0.1%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tetraparesis  | 1 (0.1%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## PRE-TREATMENT FINDINGS

### Urinary risk factors at baseline

All patients performed initial 24-hour urine analysis.

Table 6 demonstrates the results of the metabolic evaluation and the presence of urinary risk factors found at baseline evaluation. Only 13 patients (1.6%) had no urinary risk factors.

The observed mean urinary oxalate excretion was 43.0±18.4 mg per 24 hours, the mean urinary calcium excretion 5.5±5.5 mmol per 24 hours and the mean urinary phosphate excretion 31.5±67.9 mmol per 24 hours. Additionally, a mean urinary uric acid excretion of 646.7±262.8 mg per 24 hours and mean urinary sodium excretion of 179.5±81.2 mmol per 24 hours was determined. The mean protein intake was 1.3±0.4 g/kg ideal weight per 24 hours, the mean urinary volume 1907.2±880.2 mL per 24 hours. Finally, the mean urinary citrate excretion was 2931.6±1758.0 µmol per 24 hours and the mean urinary pH 6.2±2.1.

In the total study population, the most frequently found urinary risk factor at baseline was an increased protein intake, which was found in 77.0% of the patients. Other urinary risk factors included increased sodium excretion which was found in 59.9%, followed by low urinary output in 59.0%, hyperoxaluria in 36.5%, hypercalciuria in 27.8%, low urinary pH in 27.9%, increased uric acid excretion in 24.2%, hypocitraturia in 20.0% and hyperphosphaturia in 15.3%.

The most common urinary risk factors in the subpopulation of calcium oxalate stones was an increased protein intake in 78.7% of the patients, followed by an increased sodium excretion in 61.9% of the patients. Hyperoxaluria was reported in 39.7% of the patients and hypercalciuria in 27.8%.

In the subpopulation of uric acid stones, increased protein intake was found in 83.8% of the patients. In 70.3% an increased sodium excretion was reported. A low urinary pH was found in 56.8%, an increased uric acid excretion in 45.9% and hyperoxaluria in 40.5%.

In the subpopulation of cystine stones, increased sodium excretion was found in 61.9% and increased protein intake was found in 57.1% of the patients. A low urinary output was reported in 42.9%.

The mean urinary parameters at baseline in patients presenting urinary risk factors at baseline can be found in table 7. In patients with hyperoxaluria, mean urinary oxalate excretion pre-treatment was 61.4±15.7mg per 24 hours. Additionally a mean pre-treatment urinary calcium excretion of 0.2±2.0 mmol per 24 hours was observed in patients with hypercalciuria and a pre-treatment mean urinary phosphate excretion of 58.9±77.5 mmol per 24 hours in patients with hyperphosphaturia. In patients with increased uric acid excretion, mean urinary uric acid excretion pre-treatment was 1000.3±213.8 mg per 24 hours and in patients with increased urinary sodium excretion, the mean urinary sodium excretion pre-treatment was 227.3±68.4 mmol per 24 hours. Furthermore, in patients with increased protein intake, mean protein intake pre-treatment was 1.4±0.4 g/kg ideal weight per 24 hours and in patients with low urinary output, mean urinary volume was 1318.1±378.4 mL per 24 hours. Finally, in patients with hypocitraturia, mean urinary citrate excretion was 818.4±465.8 µmol per 24 hours and in patients with low urinary pH, mean urinary pH was 5.1±0.2.

Table 6: mean urinary parameters and presence of urinary risk factors at baseline

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total study population (n = 835) | Calcium oxalate stones (n = 370) | Uric acid stones (n = 37) | Cystine stones (n = 21) | Mixed stones (n = 19) | Calcium phosphate stones (n = 14) | Struvite stones(n = 11) | Brushite stones (n = 10) |
| URINARY PARAMETERS |
| **Urinary oxalate excretion,** mean±SD (mg/24h)  | 43.0±18.4 | 44.1±18.3 | 47.0±21.7 | 44.5±17.5 | 42.3±19.4 | 40.2±14.9 | 35.6±13.8 | 50.2±12.8 |
| **Urinary calcium excretion,** mean±SD ((mmol/24h) | 5.5±5.5 | 5.5±3.3 | 4.1±2.7 | 5.5±9.5 | 5.9±3.3 | 6.8±3.6 | 4.9±3.3 | 10.2±4.7 |
| **Urinary phosphate excretion,** mean±SD (mmol/24h) | 31.5±67.9 | 31.8±11.9 | 32.0±14.2 | 26.2±8.9 | 73.2±205.4 | 32.1±13.5 | 27.9±12.2 | 41.8±14.6 |
| **Urinary uric acid excretion,** mean±SD (mg/24h) | 646.7±262.8 | 669.8±238.6 | 790.3±416.7 | 508.1±170.2 | 572.4±199.9 | 697.8±196.4 | 540.9±117.3 | 639.1±203.3 |
| **Urinary sodium excretion,** mean±SD (mmol/24h) | 179.5±81.2 | 184.4±81.8 | 214.4±109.6 | 182.7±66.1 | 155.2±59.7 | 183.2±56.6 | 150.5±58.5 | 212.7±65.5 |
| **Protein intake,** mean±SD (g/kg ideal weight per 24h) | 1.3±0.4 | 1.3±0.4 | 1.5±0.5 | 1.1±0.3 | 1.3±0.4 | 1.5±0.4 | 1.2±0.4 | 1.2±0.4 |
| **Urinary volume,** mean±SD (mL/24h) | 1907.2±880.2 | 1837.5±840.8 | 2032.3±790.2 | 2473.3±1133.9 | 2294.2±915.7 | 1982.1±776.0 | 2747.3±1475.1 | 2820.0±1484.9 |
| **Urinary citrate excretion,** mean±SD (µmol/24h)  | 2931.6±1758.0 | 3021.2±1750.4 | 3187.6±2136.9 | 3414.8±1345.9 | 2744.1±1529.9 | 1984.3±1388.1 | 1326.4±1088.9 | 2421.7±1213.2 |
| **Urinary pH,** mean±SD  | 6.2±2.1 | 6.1±0.8 | 5.7±1.0 | 7.4±1.0 | 6.5±0.8 | 6.7±0.4 | 7.1±0.5 | 6.2±0.7 |
| URINARY RISK FACTORS |
| Hyperoxaluria, n(%) | 305 (36.5%) | 147 (39.7%) | 15 (40.5%) | 8 (38.1%) | 5 (26.3%) | 5 (35.7%) | 4 (36.4%) | 6 (60.0%) |
| Hypercalciuria, n(%)  | 236 (27.8%) | 103 (27.8%) | 7 (18.9%) | 5 (23.8%) | 7 (36.8%) | 9 (64.3%) | 4 (36.4%) | 7 (70.0%) |
| Hyperphosphaturia, n(%)  | 128 (15.3%) | 67 (18.1%) | 8 (21.6%) | 0  | 2 (10.5%) | 1 (7.1%) | 1 (9.1%)  | 4 (40.0%) |
| Increased uric acid excretion, n(%)  | 202 (24.2%) | 101 (27.3%) | 17 (46.0%) | 0 | 3 (15.8%) | 6 (42.9%) | 1 (9.1%) | 2 (20.0%) |
| Increased sodium excretion, n(%)  | 500 (59.9%) | 229 (61.9%) | 26 (70.3%) | 13 (61.9%) | 10 (52.6%) | 8 (57.1%) | 6 (54.6%) | 8 (80.0%) |
| Increased protein intake, n(%)  | 643 (77.0%) | 291 (78.7%) | 31 (83.8%) | 12 (57.1%) | 15 (79.0%) | 12 (85.7%) | 8 (72.7%) | 7 (70.0%) |
| Low urinary output, n(%)  | 493 (59.0%) | 224 (60.5%) | 18 (48.7%) | 9 (42.9%) | 9 (47.4%) | 8 (57.1%) | 5 (45.5%) | 3 (30.0%) |
| Hypocitraturia, n(%)  | 167 (20.0%) | 63 (17.0%) | 7 (18.9%) | 1 (4.8%) | 2 (10.5%) | 5 (35.7%) | 7 (63.6%) | 3 (30.0%) |
| Low urinary pH, n(%)  | 233 (27.9%) | 100 (27.0%) | 21 (56.8%) | 0 | 1 (5.3%) | 0 | 0 | 2 (20.0%) |

Table 7: mean urinary parameters pre-treatment in patients presenting urinary risk factors at baseline

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total study population | Calcium oxalate stones | Uric acid stones | Cystine stones | Mixed stones  | Calcium phosphate stones | Struvite stones | Brushite stones |
| **Hyperoxaluria,** mean±SD (mg/24h)  | 61.4±15.7 | 61.4±14.3 | 68.3±17.8 | 60.8±17.2 | 68.6±14.2 | 54.8±10.9 | 50.5±4.1 | 58.2±9.7 |
| **Hypercalciuria,** mean±SD (mmol/24h) | 10.0±7.6 | 9.7±3.6 | 8.9±1.6 | 15.8±20.1 | 9.6±2.7 | 7.5±3.6 | 9.7±3.7 | 12.7±6.0 |
| **Hyperphosphaturia,** mean±SD (mmol/24h) | 58.9±77.5 | 51.5±10.2 | 52.4±13.9 | NA | 490.9±606.9 | 66.0  | 59.4  | 57.1±6.4 |
| **Increased uric acid excretion,** mean±SD (mg/24h) | 1000.3±213.8 | 975.5±157.1 | 1072.2±419.4 | NA | 912.0±134.2 | 881.5±112.0 | 785.0 | 930.0±176.8 |
| **Increased sodium excretion,** mean±SD (mmol/24h) | 227.3±68.4 | 231.2±69.1 | 258.1±102.0 | 225.2±29.4 | 201.9±37.0 | 221.5±42.7 | 194.0±32.0 | 229.4±62.6 |
| **Increased protein intake,** mean±SD (g/kg ideal weight per 24h) | 1.4±0.4 | 1.4±0.3 | 1.6±0.5 | 1.3±0.2 | 1.4±0.3 | 1.6±0.3 | 1.34±0.26 | 1.4±0.2 |
| **Low urinary output,** mean±SD (mL/24h) | 1318.1±378.4 | 1274.2±376.0 | 1423.1±315.1 | 1548.9±413.5 | 1468.9±299.4 | 1416.3±347.6 | 1534.0±279.7 | 1360.0±242.5 |
| **Hypocitraturia,** mean±SD (µmol/24h)  | 818.4±465.8 | 860.5±443.1 | 719.6±504.9 | 1440.0 | 611.0±524.7 | 692.8±529.4 | 744.6±545.6 | 1294.7±144.5 |
| **Low urinary pH,** mean±SD  | 5.1±0.2 | 5.1±0.2 | 5.1±0.1 | NA | 5.0 | NA | NA | 5.3±0.4 |

### Pre-treatment rates

#### Symptomatic renal colic rate

In 779 patients with nephrolithiasis but without nephrocalcinosis and with sufficient data, the pre-treatment rates could be calculated, results of which can be found in table 8. If taken into account all stone compositions, the mean symptomatic renal colic rate was 1.7±3.0 per year and the median was 0.6 (0.2-2.1) per year.

The highest mean symptomatic renal colic rate was found in the subpopulation of mixed stones with a mean rate of 3.2±12.4 per year. The lowest was found in the brushite and struvite stone subpopulation with a mean rate of 1.0±1.2 per year and 1.0±1.6 per year respectively.

Taking into account the median symptomatic renal colic rates, the highest was found in the subpopulation of calcium phosphate stones with a median rate of 1.0 (0.2-2.2) per year, while the lowest was found in the struvite stone subpopulation with a median rate of 0.3 (0.1-1.0) per year*.*

#### Stone formation rate

In 732 patients with nephrolithiasis but without nephrocalcinosis and with sufficient data, the pre-treatment rates could be calculated, results of which can be found in table 8.

If taken into account all stone compositions, the mean stone formation rate was 0.7±0,9 per year. The highest mean stone formation rate was found in the calcium-oxalate stones group with a mean rate of 0.8±1.1 per year. The lowest was found in the mixed stone subpopulation with a mean rate of 0.4±0.4 per year.

The median stone formation rate taking into account all stone compositions, was 0.4 (0.2-0.8) per year. The highest median stone formation rate was found in the uric acid, calcium phosphate and brushite stones group with a median rate of 0.5 (0.2-1.0), 0.5 (0.3-0.8) and 0.5 (0.2-0.9) per year respectively. The lowest was found in the mixed stone subpopulation with a median rate of 0.2 (0.2-0.5) per year.

#### Urological intervention rate

In 780 patients with nephrolithiasis but without nephrocalcinosis and with sufficient data, the pre-treatment rates could be calculated, results of which can be found in table 8.

Taken into account all available patients who met these criteria, the mean urological intervention rate was 0.5±1.7 per year. The highest mean urological intervention rate was found in the subpopulation of uric acid stones with a mean rate of 1.4±5.9 per year. The lowest was found in the brushite stone subpopulation with a mean rate of 0.1±0.2 per year.

The median urological intervention rate for all stone compositions was 0.0 (0.0-0.1) per year. The same median urological intervention rate was found in calcium oxalate, uric acid, brushite and calcium phosphate stones. Whilst a median stone formation rate of 0.0 (0.0-1.1) was found in struvite stones and a median rate of 0.0 (0.0-0.0) was found in cystine and mixed stone compositions.

An overview of the pre-treatment urological interventions can be found in Table 9. The most common interventions pre-treatment were ESWL (52.6%) , followed by URS (26.8%) and double J stents (10.4%). Other procedures were PNL (7.8%), open surgery (0.8%), nephrostomy (0.6%) , bladder stone lithotripsy (0.4%), (partial) nephrectomy (0.2%) and bladder stone cystotomy (0.1%).

Table 8: pre-treatment rates of the whole study population, excluding those with nephrocalcinosis

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total study population | Calcium oxalate stones | Uric acid stones | Cystine stones | Mixed stones  | Brushite stones  | Calcium phosphate stones  | Struvite stones  |
| **SYMPTOMATIC RENAL COLIC RATE**  |
| Number of patients | 779 | 356 | 34 | 17 | 16 | 10 |  9 | 8 |
| Mean±SD (per yr)Median (IQR) (per yr) | 1.7±3.00.6 (0.2-2.1) | 1.7±3.40.6 (0.2-2.0) | 1.7±2.90.5 (0.2-1.9) | 1.5±10.70.7 (0.2-2.5) | 3.2±12.40.6 (4.4-0.2) | 1.0±1,20.4 (0.2-1.7) | 1.2±1.11.0 (0.2-2.2) | 1.0±1,60.3 (0.1-1.0) |
| **STONE FORMATION RATE**  |
| Number of patients | 732 | 328 | 32 | 17 | 16 | 10 | 10 | 8 |
| Mean±SD (per yr)Median (IQR) (per yr) | 0.7±0.90.4 (0.2-0.8) | 0.8±1.10.4 (0.2-0.9) | 0.7±0.70.5 (0.2-1.0) | 0.5±0.60.4 (0.2-0.4) | 0.4±0,40.2 (0.2-0.5) | 0.6±0.40.5 (0.2-0.9) | 0.5±0.30.5 (0.3-0.8) | 0.6±0.60.4 (0.2-0.8) |
| **UROLOGICAL INTERVENTION RATE**  |
| Number of patients | 780 | 356 | 35 | 17 | 16 | 10 | 11 | 8 |
| Mean±SD (per yr)Median (IQR) (per yr) | 0.5±1.70.0 (0.0-0.1) | 0.4±1.40.0 (0.0-0.1) | 1.4±5.90.0 (0.0-0.1) | 0.6±1.60.0 (0.0-0.0) | 0.0±0.00.0 (0.0-0.0) | 0.1±0.20.0 (0.0-0.1) | 0.4±1.10.0 (0.0-0.1) | 0.9±1.70.0 (0.0-1.1) |

Table 9: types of urological interventions in patients with nephrolithiasis, excluding those with nephrocalcinosis

|  |  |  |
| --- | --- | --- |
|  | Urological interventions before first consultation (n = 944) | Urological interventions during follow-up (n= 94) |
| ESWL | 498 (52.8%) | 38 (45.3%) |
| URS | 253 (26.8%) | 38 (45.2%) |
| JJ stent  | 98 (10.4%) | 10 (10.6%) |
| PNL  | 74(7.8%) | 6 (6.4%) |
| Nephrostomy | 6 (0.6%) | 1 (1.1%) |
| Bladder stone lithotripsy  | 4 (0.4%) | 0 |
| (Partial) nephrectomy | 2 (0.2%) | 0 |
| Open surgery  | 8 (0.8%) | 0 |
| Bladder stone cystostomy  | 1 (0.1%) | 1 (1.1%) |

## POST-TREATMENT FINDINGS

### Evolution of the urinary risk factors

The mean urinary parameters pre- and post-treatment can be found in table 10 for patients with at least six months of follow-up and in table 11 for patients with at least six months of follow-up who presented urinary risk factors at baseline.

In all patients with at least six months of follow-up, combined preventive measures significantly reduced urinary sodium excretion (*P*<0.05), calciuria (*P*<0.0001), uricosuria(*P*<0.0001) and phosphaturia (*P*<0.005). Additionally, a significant increase in urinary volume (*P*<0.0001) was determined.

In patients with hyperoxaluria and increased protein intake at baseline evaluation, combined preventive measures significantly reduced urinary oxalate excretion (*P*<0.0001) and protein intake (*P*<0.0001). Furthermore, a significant increase in patients with hypocitraturia and low urinary pH at baseline in urinary citrate excretion (*P*<0.0001) and urinary pH (*P*<0.0001) could be demonstrated.

Table 10: urinary risk factors pre- and posttreatment in the entire study population with >6 months follow-up (n=355)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean±SD  | Median (IQR) | *P*-value |
| **Urinary oxalate excretion**  Pre-treatment (mg/24h)  Post-treatment (mg/24h) | 44.3±16.944.8±18.6 | 41.0 (33.0-54.0)42.0 (33.0-53.0) | 0.9008 |
| **Urinary calcium excretion**  Pre-treatment (mmol/24h) Post-treatment ((mmol/24h) | 5.9±5.74.7±2.9 | 4.9 (3.0-7.3)4.2 (2.7-6.2) | <0.0001 |
| **Urinary phosphate excretion**  Pre-treatment (mmol/24h) Post-treatment (mmol/24) | 31.2±13.228.9± 11.1 | 28.8 (22.9-37.1)28.1 (21.1-35.8) | 0.0016 |
| **Urinary uric acid excretion**  Pre-treatment (mg/24h) Post-treatment (mg/24h) | 658.7±271.1572.6±227.8 | 617.0 (472.0-792.0)540.5 (421.0-693.0) | <0.0001 |
| **Urinary sodium excretion**  Pre-treatment (mmol/24h)Post-treatment (mmol/24h) | 187.6±81.0 175.3±77.8 | 178.0 (135.0-228.0)164.0 (120.0-215.0) | 0.0276 |
| **Protein intake**  Pre-treatment (g/kg ideal weight per 24h)Post-treatment (g/kg ideal weight per 24h) | 1.4±0.41.4±0.4 | 1.3 (1.1-1.6)1.3 (1.1-1.6) | 0.2262 |
| **Urinary volume**  Pre-treatment (mL/24h)Post-treatment (mL/24h) | 2094.5±903.42382.2±869.8 | 1950.0 (1400.0-2600.0)2300.0 (1790.0-2850.0) | <0.0001 |
| **Urinary citrate excretion**  Pre-treatment (µmol /24h) Post-treatment (µmol /24h) | 2940.4±1876.63231.9±2298.8 | 2687.5 (1567.0-4014.0)2760.0 (1710.0-4290.0) | 0.0533 |
| **Urinary pH**  Pre-treatment  Post-treatment | 6.2±0.96.2±0.9 | 6.0 (5.2-7.0)6.1 (5.4-7.0) | 0.4338 |

Table 11: urinary parameters pre- and posttreatment in patients with >6 months follow-up with urinary risk factors at baseline

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean±SD | Median (IQR) | *P-*value  |
| **Urinary oxalate excretion (n= 136)**  Pre-treatment (mg/24h) Post-treatment (mg/24h) | 60.1±13.749.2±20.8 | 65.0 (59.0-73.0)46.0 (36.0-57.0) | <0.0001 |
| **Urinary calcium excretion (n=114)**  Pre-treatment (mmol/24h) Post-treatment (mmol/24h) | 10.1±7.76.0±2.8 | 8.7 (7.0-2.5)7.8 (5.7-6.0) | <0.0001 |
| **Urinary phosphate excretion (n=54)**  Pre-treatment (mmol/24h) Post-treatment (mmol/24h) | 54.6±13.037.6±13.5 | 51.3 (45.4-59.2)36.8 (28.6-43.6) | <0.0001 |
| **Urinary uric acid excretion (n=95)**  Pre-treatment (mg/24h) Post-treatment (mg/24h) | 995.0±240.5709.3±254.6 | 981.5 (823-1133)662.0 (525.0-774.0) | <0.0001 |
| **Urinary sodium excretion (n=228)**  Pre-treatment (mmol/24h)Post-treatment (mmol/24h) | 228.0±70.3192.2±77.1 | 206.0 (180.0-259.0)180.5 (133.0-230.5) | <0.0001 |
| **Protein intake (n=288)**  Pre-treatment (g/kg ideal weight per 24h)Post-treatment (g/kg ideal weight per 24h) | 1.5±0.4 1.4±0.4 | 1.4 (1.2-1.7)1.3 (1.1-1.6) | 0.0005 |
| **Urinary volume (n=182)**  Pre-treatment (mL/24h)Post-treatment (mL/24h) | 1422.8±352.62045.0±788.5 | 1400.0 (1200.0-1730.0)1962.5 (1540.0-2550.0) | <0.0001 |
| **Urinary citrate excretion (n=92)**  Pre-treatment (µmol/24h) Post-treatment (µmol/24h) | 750.1±474.92069.5±1918.3 | 723.0 (254.0-1220.0)1480.0 (643.0-2339.0) | <0.0001 |
| **Urinary pH (n= 110)** Pre-treatment Post-treatment  | 5.0±0.1 5.9±0.9 | 5.0 (5.0-5.0)5.9 (5.0-5.9) | <0.0001 |

### Post-treatment rates

#### Post-treatment symptomatic renal colic rate

To be able to compare the pre- and posttreatment symptomatic renal colic rate, only patients with more than 12 months of clinical follow-up were taken into account, excluding those with nephrocalcinosis.

Table 12 shows that 256 patients met those criteria (162 men; 94 women), with a median follow-up period of 2.9 years (1.6-5.4). The mean pre-treatment symptomatic renal colic rate in those patients was 0.4±1.1 per year and the median 0.1 (0.0-0.4) per year . The mean post-treatment symptomatic renal colic rate was 0.2±0.3 per year and the median 0.0 (0.0-0.1) per year.The Wilcoxon rank test showed a significant reduction (*P*<0.0001)*.*

#### Post-treatment stone formation rate

Stone formation rates were calculated for patients who had more than 12 months of clinical and medical imaging follow-up, excluding those with nephrocalcinosis. Only the consultations up to the last medical imaging performed were taken into account.

In table 12, the actual pre-treatment interval was used and 142 patients could be analysed (84 men and 58 women), with a median follow-up period of 2.8 (1.6-4.9) years. The mean pre-treatment stone formation rate was 3.7±13.3 per year and the median 0.5 (0.2-1.6) per year. The mean post-treatment stone formation rate was 0.8±1.2 per year and the median 0.4 (0.0-1.0) per year. Thus, a significant reduction could be demonstrated (*P*<0.05).

Additional calculations where pre-treatment rates were adjusted are shown in Table 13. If the stone formation rate is expressed over five years in patients with less than five years pre-treatment interval, the mean pre-treatment stone formation rate was 0.7±0.9 per year and the median 0.4 (0.2-0.8) per year. The mean post-treatment stone formation rate was 0.8±1.2 per year and the median 0.4 (0.0-1.0) per year. No significant difference could be demonstrated (p=0.2). If only taking into account patients with a pre-treatment interval longer than three years, the mean pre-treatment stone formation rate was 0.7±0.9 per year and the median 0.4 (0.2-0.8) per year. The mean post-treatment stone formation rate was 0.8±1.2 per year and the median 0.4 (0.0-1.0) per year. No significant difference could be demonstrated (p=0.5).

#### Post-treatment urological intervention rate

To be able to compare the pre- and posttreatment urological intervention rate, only patients with more than 12 months of clinical follow-up were taken into account, excluding those with nephrocalcinosis. As shown in table 12, 254 patients met those criteria (161 men; 93 women), with a median follow-up period of 2.9 years (1.6-5.4). The mean pre-treatment urological intervention rate was 0.6±2.2 per year and the median 0.0 (0.0-0.2) per year. The mean post-treatment urological intervention rate was 0.1±0.3 per year and the median 0.0 (0.0-0.0) per year. Consequently, a Wilcoxon signed rank test demonstrated a significant reduction (*P*<0.0001).

An overview of the urological interventions performed during follow-up can be found in Table 9. The most common interventions during follow-up at the kidney stone prevention clinic were ESWL and URS, each of which was equally common (4.2%). The second most common were double J stents (10.6%), followed by PNL (6.4%), nephrostomy (1.1%) and bladder stone cystostomy (1.1%).

Table 12: Wilcoxon signed rank test in patients with at least 12 months follow-up and excluding those with nephrocalcinosis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean±SD | Median (IQR) | *P*-value |
| **SYMPTOMATIC RENAL COLIC RATE (n=256)** |
| Follow-up period (yr) | 3.7±2.6 | 2.9 (1.6-5.4) | <0.0001 |
| Pre-treatment rate (per yr)Post-treatment rate (per yr) | 0.4±1.10.2±0.3 | 0.1 (0.0-0.4)0.0 (0.0-0.1) |
| **STONE FORMATION RATE (n=142)** |
| Follow-up period (yr) | 3.5±2.3 | 2.8 (1.6-4.9) | 0.0061 |
| Pre-treatment rate (per yr)Post-treatment rate (per yr) | 3.7±13.3 0.8±1.2 | 0.5 (0.2-1.6)0.4 (0.0-1.0) |
| **UROLOGICAL INTERVENTION RATE (n=254)** |
| Follow-up period (yr) | 3.7±2.6 | 2.9 (1.6-5.4) | <0.0001 |
| Pre-treatment rate (per yr)Post-treatment rate (per yr) | 0.6±2.20.1±0.3 | 0.0 (0.0-0.2)0.0 (0.0-0.0) |

Table 13: Additional Wilcoxon signed rank tests for stone formation rate with the intent of avoiding overestimation of the pre-treatment rates

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean ± SD | Median (IQR) | *P*-value |
| **EXPRESSION OF THE STONE FORMATION RATES BASED ON A MINIMUM PRETREATMENT INTERVAL OF 5 YEARS (n = 142)a** |
| Pre-treatment rate (per yr)Post-treatment rate (per yr) | 0.7±0.9 0.8±1.2 | 0.4 (0.2-0.8)0.4 (0.0-1.0) | 0.2349 |
| **CONSIDERING ONLY PATIENTS WITH A PRE-TREATMENT INTERVAL OF MORE THAN 3 YEARS (n = 90 )b** |
| Pre-treatment rate (per yr)Post-treatment rate (per yr) | 0.7±0.90.8±1.2  | 0.4 (0.2-0.8)0.4 (0.0-1.0) |  0.4919 |

a: pre-treatment interval was arbitrarily changed to 5 years in all patients with shorter pre-treatment follow up to avoid overestimation of pre-treatment stone formation rates.

b: only patients with at least 3 years of pre-treatment follow up were included in the analysis.

# DISCUSSION

This retrospective analysis had the objective to evaluate the effect of combined preventive measures on urinary risk factors for kidney stone formation in patients with nephrolithiasis and/or nephrocalcinosis followed at the kidney stone prevention clinic of the UZ Brussel. Additionally, the effect on incidence rates of symptomatic renal colic episodes, kidney stone formation and the performance of urological procedures in patients with nephrolithiasis was evaluated.

The demographic characteristics of our study population were comparable to previous reports. Our study population consisted mainly of patients of Caucasian and Middle East descent and included only eight Asian and nine Black patients. Although Asian ethnicity is rare amongst a Belgian patient population, it is known that the prevalence of nephrolithiasis is lower in the Asian population (2). The same is true for the African-American population (52), however there is a paucity of data regarding the prevalence of nephrolithiasis in Black patients originating from sub-Saharan Africa.

According to the literature, the diagnosis of nephrolithiasis is usually made in the fifth decade (51). In our study population, the diagnosis of nephrolithiasis/nephrocalcinosis was made at a median age of 36.0 years (25.0-49.0). The age of first consultation at the kidney stone prevention clinic (median 47.0 years) was similar to previous reports (46). The median interval between the diagnosis of nephrolithiasis/nephrocalcinosis and the first consultation at the kidney stone clinic was 3.7 years (0.4-12.1). With this IQR, it should be noted that in a large proportion of patients there is a long interval between the diagnosis and the first consultation. A possible reason for this is that the importance of kidney stone prevention is not yet realised by all referring physicians.

In our study, the male to female ratio was 1.8, which is comparable to the ones reported by Parks and Coe (1.9) (46) and Daudon et al. (2.2) (53). It is known that the female proportion of nephrolithiasis patients is increasing. Scales et al. demonstrated a decrease in male to female ratio from 3.1 to 1.3 between 1970 and 2000 and attributed this to the rising trend in obesity and type 2 diabetes, which increases especially in women when lifestyle and eating habits change (54).

The distribution in stone composition was similar to the one described by Parks and Coe (46) and a study concerning the epidemiological data on nephrolithiasis in Belgium (55). Exceptions to this were calcium phosphate stones, which were found less frequently in our study (5.0% in our population vs 10.1% in the study of Parks and Coe and 14.0% in the Belgian epidemiological study) and cystine stones that were found more frequently (4.4% in our population vs 2.1% in the study of Parks and Coe and 0.4% in the Belgian epidemiological study).

The relationship between obesity and a higher risk of nephrolithiasis is well known (10-12). This was also demonstrated in our study where the mean BMI of our population was 26.7 kg/m² and 24.4% of the patients were obese. Associated mechanisms for this are a lower urinary pH, induced by insulin resistance and predisposing for the development of uric acid calculi, and an increased urinary uric acid, sodium, oxalate, calcium and phosphorus excretion, all of which are urinary risk factors for stone formation (12,56).

The prevalence of gastro-intestinal problems, renal distal tubular acidosis and hyperparathyroidism in our cohort was similar to the study by Parks and Coe (46). As previously reported by Pearl et al. (7), we also observed in our study that ESWL accounts for the majority of urological interventions, followed shortly after by URS, this at the expense of open surgery.

A first research question addressed in this study was to what extent preventive measures influenced urinary risk factors involved in stone formation. Urinary risk factors are important determinants of kidney stone formation. The first step in lithogenesis is the formation of crystals in the urine, also known as crystalluria, due to urine supersaturation. These crystals can subsequently aggregate and evolve to kidney stones.

A possible cause of crystal formation is an excessive concentration of a substance in the urine, either due to an excessive intake of nutrients or medication, or to excessive endogenous production. A second way to achieve so-called supersaturation is by insufficient urinary output. However, occasionally stone formation can occur with normal solute concentrations when abnormal urinary pH reduces their solubility and promotes precipitation of crystals. To prevent stone formation, first urinary excretion of stone components such as oxalate, calcium, phosphate or uric acid has to be kept as low as possible. On the other hand urinary output has to be increased in order to avoid supersaturation. Urinary citrate also plays an important role as a crystallisation inhibitor of calcium salts and its concentration must be kept high enough. Animal proteins and sodium excretion also contribute to stone formation by increasing calcium excretion and reducing citrate concentration in the urine (57).

At baseline, 835 patients with nephrolithiasis or nephrocalcinosis were assessed for urinary risk factors. The most commonly reported risk factors were an increased protein intake (77.0%), increased sodium excretion (59.9%) and low urinary output (59.0%). The baseline urinary risk factors were found in a similar percentage of patients compared to values found in the literature (44,58-62). Exceptions were hypercalciuria, which was slightly less common in our population (27.8% in our study population vs 33.0%-43.0% in other studies), and an increased sodium excretion, which was found more common (59.9% in our study population vs 24.3% in other studies). However, it should be noted that our definition of increased sodium excretion was >150.0 mmol/24h while that of the other studies was >200.0 mmol/24h. Also, it is worth noting that these are the abnormalities expected in a Western diet that is typically too high in salt and protein, which may help explain the increasing prevalence of nephrolithiasis.

A significant reduction of the urinary sodium, calcium, phosphate and uric acid excretion was observed after start of preventive measures in the overall cohort with at least six months of clinical and biochemical follow-up. In addition, follow up at the stone clinic was associated with a significant increase in urinary volume. There was no significant change in the urinary oxalate excretion, urinary citrate excretion and protein intake in the overall population with more than six months of follow-up. However, in patients who presented hyperoxaluria, hypocitraturia, increased protein intake and low urinary pH at baseline, a significant reduction in urinary oxalate excretion and protein intake as well as a significant increase in urinary pH and urinary citrate excretion was observed during follow up. This illustrates that extra guidance and emphasis on certain preventive measures tailored to the underlying metabolic abnormality does have positive effects. This conclusion is also supported by other studies which compared tailored to general dietary or pharmaceutical measures and concluded tailored preventive measures to be more effective (44-46).

Other aims of this study were to examine to what extent preventive measures influenced the rates of symptomatic renal colic, stone formation and urological intervention in patients with nephrolithiasis. The symptomatic renal colic rates and urological intervention rate are of clinical importance for the patients given that they reflect the burden that patients experience on annual basis from nephrolithiasis. The importance of the stone formation rate should not be underestimated either, considering that it includes analysis of asymptomatic stone formation, which also play a key role in the burden of nephrolithiasis. As stated before, it was demonstrated by the cohort study by Boyce et al. (5) that 20.5% of asymptomatic nephrolithiasis patients experienced at least one symptomatic renal colic episode in the following ten years of follow-up. Thus, reducing the amount of asymptomatic nephrolithiasis should also be one of the goals of a kidney stone prevention programme.

The present cohort study clearly showed a significant reduction in renal colic rate and urological intervention rate after implementing combined preventive measures in patients with nephrolithiasis. This is in accordance with the previously reported findings by Parks and Coe (47).

However, our study does not provide an unequivocal answer to the research question of whether the stone formation rate can be significantly reduced by implementing combined preventive measures. This ambiguity results from the difficulty to correctly estimate the stone formation rate in the period before the follow up at the stone clinic was started. Referral to the stone clinic often occurs after removal of multiple stones over a relatively short period although these stones might have formed over several years. This can result in an overestimation of the stone formation rate before start of the follow up and a bias towards overestimating the protective effect of follow up at the stone clinic. Without adjustment for the follow up period before attending the stone clinic we indeed observed a significant reduction of the stone formation rate (*P*<0.01). This confirms the results of Parks and Coe who applied the same methodology for the calculations (47). In order to avoid potential bias due to short treatment interval we performed to adjusted calculations of the stone formation rate. In one we arbitrarily calculated pre-treatment rates based on follow up times of five years in patients with less than five years pre-treatment interval. In the second analysis we only included patients with at least three years pre-treatment follow up. Contrary to the unadjusted analysis we could not confirm a significant reduction in the stone formation rate in the adjusted analyses (p=0.2 and 0.5respectively). We can therefore conclude that although the stone formation rate decreased after follow up at the stone clinic it is not excluded that this might be the result of bias secondary to underestimating the time required for stone formation before follow up at the stone clinic. The retrospective nature of the present study does not provide an optimal way to assess this outcome, especially as this rate could be determined in a lower number of patients compared to the other rates.

However, it should also be mentioned that the importance of preventive medical therapy to reduce the stone formation rates in patients with and without residual stone fragments after ESWL and PNL was previously demonstrated (45-46). These studies did not encounter the same problem of pre-treatment rates as they compared a group of patients who implemented medical therapy to those who did not. We can therefore conclude that although there is no unambiguous answer to the question of whether we were able to statistically significantly reduce stone formation rates in this study, lowering this rate should be an important objective pursued by kidney stone prevention programmes given the clinical importance indicated before.

By reducing the number of urological interventions and symptomatic renal colics, we expect not only that the costs related to nephrolithiasis will decrease, but also that the quality of life of the patients will improve. After all, it has previously been shown that it is mainly in patients with a higher number of spontaneously passed stones or number of procedures that the quality of life decreased (20).

Kidney stone patients have an increased risk of developing ESRD (17) and this risk is higher in recurrent stone formers compared to incident stone formers (18). Therefore, a reduction in the progression to ESRD can also be expected after implementation of kidney stone prevention, as our study shows that a decrease in recurrence rates can be expected. Further research is needed to confirm this assumption and to determine the effect on other associated diseases as well.

Reducing stone recurrence and urological intervention rates could logically improve not only the associated morbidity and reduced quality of life of kidney stone patients, but also the healthcare- related costs. As mentioned before, the retrospective analysis of the use of healthcare resources by Pearl et al. (7) quantified the economic burden of nephrolithiasis in the United States. Direct costs consisted mainly of emergency room visits, hospitalizations, medical imaging, urological interventions and follow-up consultations. Our study demonstrates a significant reduction in symptomatic renal colic rates, which could logically lead to a decrease in the number of emergency room visits. The same reasoning can be applied to the number of urological interventions as a consequence of the reduced urological intervention rates.

Since kidney stone prevention can reduce both the number of renal colics and urological interventions patients experience, it could also result in a lower hospitalisation duration and leave of absences. Thus, not only the direct, but also the indirect costs related to kidney stones could be reduced. According to Pearl et al. (7), these mainly consisted of hours of work lost. Therefore, we can conclude that kidney stone prevention could presumably not only benefit individual patients but also the whole society. However, further research is needed to confirm and quantify this.

The present study investigated a large cohort of patients, which led to reliable effect estimate and sufficient statistically power for hypothesis testing. In contrast to most previous studies, our approach was innovating because it investigated the combined effect of multiple preventive measures on several clinically relevant outcomes in a real-life setting. Patients were closely monitored according to the European Association of Urology guidelines, that can be easily implemented in everyday practice and understood by people who have not often come into contact with the kidney stone prevention field before.

Our study has several inherent weaknesses. First of all, it is a retrospective study, which entails an inferior level of evidence compared with prospective studies. However, contrary to clinical trials, this methodological choice has the advantage of illustrating what actually happens in everyday clinical practice. There was no control population available, which is why we worked with rates and compared them before and after preventive measures were established. For this, we used all available data stated in the patient’s medical file and complemented this by data collected during anamnesis.

In order to avoid overestimating the pre-treatment stone formation ratio, three different types of analysis were used to assess the kidney stone formation rate. However, it remains impossible to know the exact time interval during which the stones visible on medical imaging were formed pre-treatment.

Thus, we must take into account a possible margin of error for the pre-treatment stone formation rate calculated, likely overestimating the pre-treatment stone formation rate. On the other hand, the pre-treatment stone formation rate is based on patient’s history being verified only once, resulting in a possible underestimation due to recall bias. Whereas the post-treatment stone formation rate will logically, given frequent follow-up with a thorough anamnesis and the use of medical imaging, give a much more correct value of the number of stones formed.

The greatest obstacle for stone prevention programmes is the high frequency of drop-outs/loss to follow-up. Thus, Parks and Coe (48) noted a yearly loss to follow-up rate of 20.0-38.0% was noted. In our study, only 42.5% of the baseline population had a minimum six months clinical and biochemical follow-up, suggesting a large proportion of drop-outs. Another interesting research topic in the future would be to determine which patient profiles are more susceptible to a loss of follow-up, as well as to investigate which interventions could be useful to lower the patient drop-out rates and when they are best applied.

Additionally, given that crystal formation precedes stone formation, it would be valuable to examine the effect of preventive measures on the crystalluria, which is a parameter already included in the database, but beyond the scope of this study to evaluate.

In order to further optimise the quality of care, research should also be carried out into software that displays clinical results, data from medical imaging, and findings from urine and blood analyses longitudinally and clearly. This could be a useful tool to show patients the effect of their efforts, which could also have a positive effect on continuity of care.

These results could be used to convince patients, in UZ Brussel as well as in other hospitals, that the investment of time and money in preventive programs is well worthwhile. On the other hand, other services such as the emergency department, general practitioners and colleagues from the urology department could be informed about the usefulness of kidney stone prevention in daily practice. This would allow more patients to be referred to the kidney stone prevention clinic for further help and shortening the time-interval between the diagnosis and first consultation.

There is also room for improvement in the organisation of kidney stone care and prevention. Within hospitals, better cooperation between different services such as the urology department, the emergency department and nephrology should be promoted. Collaborations between different hospitals can also be beneficial for nephrolithiasis prevention. A study by Lingeman et al. (63) demonstrated that when the Chicago research centre of Parks and Coe networked with other treatment centres, similar results could be obtained in these centres as well. This shows that combining forces and expertise could lead to reaching more patients, thus increasing the impact and scale of kidney stone prevention programmes in Belgium.

# CONCLUSION

By analysing the data from the patient database of the kidney stone prevention clinic, this thesis demonstrates that combined preventive measures have a significant effect on reducing the urinary risk factors in patients with nephrolithiasis and nephrocalcinosis, especially when tailored to the patient’s initial metabolic evaluation.

This research also aimed to identify the effect of kidney stone prevention on clinically significant outcomes for the patient, including symptomatic renal colic rate, urological intervention rate and stone formation rate. The results indicate that symptomatic renal colic rates and urological intervention rates can significantly be reduced in patients with nephrolithiasis after implementing combined preventive measures. Additionally, the same effect can be expected on the stone formation rate, but no unambiguous answer to this research question could be given.

Based on these conclusions, practitioners should refer nephrolithiasis and nephrocalcinosis patients to a kidney stone prevention programme, to reduce both the recurrence rate and associated health care burden of nephrolithiasis. A reduction in healthcare costs related to nephrolithiasis can also be expected, for the benefit of individual patients as well as society as a whole.

However, it also became clear that continuing to motivate patients to remain in follow-up is a major bottleneck. Further research should examine which patients are most susceptible to loss of follow-up and how these loss to follow-up rates could be improved. Other topics that should be addressed are the effect of these combined preventive measures in primary prevention and on the diseases associated with nephrolithiasis and nephrocalcinosis such as ESRD and CKD. Furthermore, the impact of kidney stone prevention on healthcare related costs should also be unravelled and quantified.

# ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to my promotor, Prof. Dr. Wissing, for his valuable guidance, contributions to the statistical analysis and the opportunity to complete my thesis in the nephrology department.

I could not have completed this thesis without the help of my co-promotor Dr. Van de Perre. Therefore, I would like to thank her for her endless patience, great accessibility and comprehensive feedback. Following her consultations has also enabled me to see the value of kidney stone prevention in practice.

Last but not least, the contributions and adjustments made to the Kidney stone prevention database by Luc Vonckx and Prof. Tielemans were indispensable and truly appreciated.

# REFERENCES

1. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of Kidney Stones in the United States. Eur Urol. 2012;62(1):160-5.
2. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y. Epidemiology of stone disease across the world. World Journal of Urology. 2017;35(9):1301-20.
3. Ahmad F, Nada M, Farid A, Haleem M, Razack S. Epidemiology of urolithiasis with emphasis on ultrasound detection: A retrospective analysis of 5371 cases in Saudi Arabia. Saudi Journal of Kidney Diseases and Transplantation. 2015;26(2):386.
4. Robertson W.G., Hughes H. Epidemiology of Urinary Stone Disease in Saudi Arabia. Urolithiasis 2. 1994;17(1):453-55.
5. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time Trends in Reported Prevalence of Kidney Stones in the United States: 1976-1994. Kidney International. 2003;63(5):1817–23.
6. Boyce CJ, Pickhardt PJ, Lawrence EM, Kim DH, Bruce RJ. Prevalence of Urolithiasis in Asymptomatic Adults: Objective Determination Using Low Dose Noncontrast Computerized Tomography. The Journal of Urology. 2010;183(3):1017-21.
7. Daudon M, Jungers P, Bazin D, Williams J. Recurrence rates of urinary calculi according to stone composition and morphology. Urolithiasis. 2018;46(5):459-70.
8. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. J Urol. 2005;173(3):848–57.
9. Antonelli JA, Maalouf NM, Pearle MS, Lotan Y. Use of the National Health and Nutrition Examination Survey to Calculate the Impact of Obesity and Diabetes on Cost and Prevalence of Urolithiasis in 2030. Eur Urol. 2014;66(4):724-9.
10. Lieske JC, de la Vega LSP, Gettman MT, Slezak JM, Bergstralh EJ, Melton LJ, III, et al. Diabetes Mellitus and the Risk of Urinary Tract Stones: A Population-Based Case-Control Study. American journal of kidney diseases. 2006;48(6):897-904.
11. Taylor EN, Stampfer MJ, Curhan GC. Obesity, Weight Gain, and the Risk of Kidney Stones. JAMA. 2005;293(4):455-62.
12. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic Syndrome and Self-Reported History of Kidney Stones: The National Health and Nutrition Examination Survey (NHANES III) 1988-1994. American journal of kidney disease. 2008;51(5):741-7.
13. Maalouf N. Metabolic Syndrome and the Genesis of Uric Acid Stones. Journal of Renal Nutrition. 2011;21(1):128-31.
14. Taylor E, Feskanich D, Paik J, Curhan G. Nephrolithiasis and Risk of Incident Bone Fracture. Journal of Urology. 2016;195(5):1482-6.
15. Yü T, Gutman AB. Uric acid nephrolithiasis in gout. Predisposing factors. Ann Intern Med. 1967;67(6):1133-48.
16. Tsai SH, Stoller ML, Sherer BA, Chao ZH, Tung TH. Risk of nephrolithiasis in patients with sleep apnea: a population-based cohort study. J Clin Sleep Med. 2018;14(5):767–73.
17. Borghi L, Meschi T, Guerra A, Briganti A, Schianchi T, Allegri F, et al. Essential arterial hypertension and stone disease. Kidney Int. 1999;55(6):2397–2406.
18. El-Zoghby ZM, Lieske JC, Foley RN, Bergstralh EJ, Li X, Melton LJ, et al. Urolithiasis and the Risk of ESRD. Clin J Am Soc Nephrol. 2012;7(9):1409-15.
19. Dhondup T, Kittanamongkolchai W, Vaughan LE, Mehta RA, Chhina JK, Enders FT, et al. Risk of ESRD and Mortality in Kidney and Bladder Stone Formers. Am J Kidney Dis. 2018;72(6):790-7.
20. Ferraro P, Taylor E, Eisner B, Gambaro G, Rimm E, Mukamal K, et al. History of Kidney Stones and the Risk of Coronary Heart Disease. JAMA. 2013;310(4):408.
21. Alexander R, Hemmelgarn B, Wiebe N, Bello A, Samuel S, Klarenbach S, et al. Kidney Stones and Cardiovascular Events: A Cohort Study. Clinical Journal of the American Society of Nephrology. 2013;9(3):506-12.
22. Reiner A, Kahn A, Eisner B, Pletcher M, Sadetsky N, Williams O, et al. Kidney Stones and Subclinical Atherosclerosis in Young Adults: The CARDIA Study. Journal of Urology. 2011;185(3):920-5.
23. Shavit L, Girfoglio D, Vijay V, Goldsmith D, Ferraro P, Moochhala S, et al. Vascular Calcification and Bone Mineral Density in Recurrent Kidney Stone Formers. Clinical Journal of the American Society of Nephrology. 2015;10(2):278-85.
24. Bensalah K, Tuncel A, Gupta A, Raman JD, Pearle MS, Lotan Y. Determinants of Quality of Life for Patients With Kidney Stones. The Journal of urology. 2008;179(6):2238-43.
25. Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petřík A, et al. Metabolic Evaluation and Recurrence Prevention for Urinary Stone Patients: EAU Guidelines. European Urology. 2015;67(4):750–63.
26. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. The Journal of Urology. 1996;155(3):839-43.
27. Massey LK. Dietary Salt, Urinary Calcium, and Kidney Stone Risk. Nutrition Reviews. 1995;53(5):131-4.
28. Taylor EN, Stampfer MJ, Curhan GC. Dietary Factors and the Risk of Incident Kidney Stones in Men: New Insights after 14 Years of Follow-up. Journal of the American Society of Nephrology. 2004;15(12):3225-32.
29. Taylor EN, Fung TT, Curhan GC. DASH-Style Diet Associates with Reduced Risk for Kidney Stones. Journal of the American Society of Nephrology. 2009;20(10):2253-9.
30. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of Two Diets for the Prevention of Recurrent Stones in Idiopathic Hypercalciuria. New England Journal of Medicine. 2002;346(2):77-84.
31. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Dietary and Lifestyle Risk Factors Associated with Incident Kidney Stones in Men and Women. J Urol. 2017;198(4):858-63.
32. Zisman AL. Effectiveness of Treatment Modalities on Kidney Stone Recurrence. Clin J Am Soc Nephrol. 2017;12(10):1699-708.
33. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. Journal of cardiovascular pharmacology. 1993;22(6):78-86.
34. Ohkawa M, Tokunaga S, Nakashima T, Orito M, Hisazumi H. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. British journal of Urology. 1992;69(6):571-6.
35. Laerum E, Larsen S. Thiazide Prophylaxis of Urolithiasis. Acta Medica Scandinavica. 1984;215(4):383-9.
36. Lojanapiwat B, Tanthanuch M, Pripathanont C, Ratchanon S, Srinualnad S, Taweemonkongsap T, et al. Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. International Brazilian journal of urology. 2011;37(5):611-6.
37. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. The Journal of Urology. 1993;150(6):1761–4.
38. Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. The Journal of Urology. 1997;158(6):2069-73.
39. Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized Trial of Allopurinol in the Prevention of Calcium Oxalate Calculi. New England Journal of Medicine. 1986;315(22):1386-9.
40. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. Kidney International. 1986;30(3):422-8.
41. Singer A, Das S. Cystinuria: A Review of the Pathophysiology and Management. The Journal of Urology. 1989;142(3):669-73.
42. Sarica K, İnal Y, Erturhan S, Yağci F. The effect of calcium channel blockers on stone regrowth and recurrence after shock wave lithotripsy. Urological Research. 2006;34(3):184-9.
43. Hosking DH, Erickson SB, Van den Berg CJ, Wilson DM, Smith LH. The stone clinic effect in patients with idiopathic calcium urolithiasis. J Urol. 1983;130(6):1115–8.
44. Iguchi M, Umekawa T, Ishikawa Y, et al. Clinical effects of prophylactic dietary treatment on renal stones. J Urol. 1990;144(2):229–32.
45. Kang D, Maloney M, Haleblian G, Springhart W, Honeycutt E, Eisenstein E, et al. Effect of Medical Management on Recurrent Stone Formation Following Percutaneous Nephrolithotomy. Journal of Urology. 2007;177(5):1785-89.
46. Fine JK, Pak CY, Preminger GM. Effect of medical management and residual fragments on recurrent stone formation following shock wave lithotripsy. J Urol. 1995;153(1):27–33.
47. Parks JH, Coe FL. Evidence for durable kidney stone prevention over several decades. BJU Int. 2009;103(9):1238–46.
48. Parks J, Asplin J, Coe F. Patient adherence to long-term medical treatment of kidney stones. The Journal of Urology. 2001 ;166(6):2057-60.
49. Hsi RS, Stoller ML. A Spectrum: Nephrocalcinosis-Nephrolithiasis. Journal of urology. 2015;194(5):1188-9.
50. Shavit L, Jaeger P, Unwin RJ. What Is Nephrocalcinosis? Kidney international. 2015;88(1):35-43.
51. Oliveira B, Kleta R, Bockenhauer D, Walsh SB. Genetic, pathophysiological, and clinical aspects of nephrocalcinosis. American journal of physiology. 2016;311(6):1243-52.
52. Kittanamongkolchai W, Vaughan L, Enders F, Dhondup T, Mehta R, Krambeck A, et al. The Changing Incidence and Presentation of Urinary Stones Over 3 Decades. Mayo Clinic Proceedings. 2018;93(3):291-9.
53. Daudon M, Hennequin C, Lacour B, Le Moel G, Donsimoni R, Fellahi S, et al. Sex- and age-related composition of 10 617 calculi analyzed by infrared spectroscopy. Urological Research. 1995;23(5):319-26.
54. Scales C, Curtis L, Norris R, Springhart W, Sur R, Schulman K, et al. Changing Gender Prevalence of Stone Disease. Journal of Urology. 2007;177(3):979-82.
55. Castiglione V, Jouret F, Bruyère O, Dubois B, Thomas A, Waltregny D, et al. Épidémiologie de la lithiase urinaire en Belgique sur base d’une classification morpho-constitutionnelle. Néphrologie & Thérapeutique. 2015;11(1):42-49.
56. Obligado S, Goldfarb D. The Association of Nephrolithiasis With Hypertension and Obesity: A Review. American Journal of Hypertension. 2008;21(3):257-264.
57. Daudon M, Jungers P, Traxer O. Lithiase urinaire. 2nd ed. Paris: Médecine sciences publications-[Lavoisier]; 2012.
58. Harvey JA, Hill KD, Pak CY. Similarity of urinary risk factors among stone-forming patients in five regions of the United States. J Lithotr Stone Dis. 1990 Apr;2(2):124-32.
59. Eisner BH, Sheth S, Dretler SP, Herrick B, Pais VM Jr. Abnormalities of 24-hour urine composition in first-time and recurrent stone-formers. Urology. 2012 Oct;80(4):776-9.
60. Spradling K, Vernez SL, Khoyliar C, Morgan JB, Okhunov Z, Preminger GM, Lipkin ME, Landman J, Youssef RF. Prevalence of Hyperoxaluria in Urinary Stone Formers: Chronological and Geographical Trends and a Literature Review. J Endourol. 2016 Apr;30(4):469-75.
61. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001 Jun;59(6):2290-8.
62. Lingeman J, Mardis H, Kahnoski R, Goldfarb DS, Lacy S, Grasso M, Scheinman SJ, Parks JH, Asplin JR, Coe FL. Medical reduction of stone risk in a network of treatment centers compared to a research clinic. J Urol. 1998 Nov;160(5):1629-34.

# ATTACHMENT 1: stone compositions according to the European Renal Stone Network Survey



# ATTACHMENT 2: ICH GCP certificate



# Afbeelding met tekst  Automatisch gegenereerde beschrijvingATTACHMENT 3: approvals of the Ethics committee

