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The Swiss Kidney Stone Cohort (SKSC), a longitudinal, multi-centric, observational cohort to study course and causes of kidney stone disease in Switzerland

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Abstract

Background: Kidney stone disease has a high prevalence worldwide of approximately 10 % of the population and is characterized by a high recurrence rate Kidney stone disease results from a combination of genetic, environmental, and life-style risk factors, and the dissection of these factors is complex. **Methods:** The Swiss Kidney Stone Cohort (SKSC) is an investigator-initiated prospective, multi-centric longitudinal, observational study in patients with kidney stones followed with regular visits over a period of 3 years after inclusion. Ongoing follow-ups by biannual telephone interviews will provide long-term outcome data. SKSC comprises 782 adult patients (age > 18 yrs) with either recurrent stones or a single stone event with at least one risk factor for recurrence. In addition, a control cohort of 207 individuals without kidney stone history and absence of kidney stones on a low-dose CT-scan at enrolment has also been recruited. SKSC includes extensive collections of clinical data, biochemical data in blood and 24 hr urine samples, and genetic data. Biosamples are stored at a dedicated biobank. Information on diet and dietary habits were collected through food frequency questionnaires and standardized recall interviews by trained dieticians with the Globodiet software. **Conclusion:** SKSC provides an unique opportunity and resource to further study cause and course of kidney disease in a large population with data and samples collected of a homogenous collective of patients throughout the whole Swiss population.

Word count: 3478 words

Introduction

Kidney stones disease affects 10-15% of the population world-wide with at least one episode per lifetime and its prevalence is increasing [1-3]. The lifetime risk to develop at least one stone episode is about 20 % for men and 10 % for women [4]. About 2-5 % of the population is suffering from recurrent symptomatic kidney stone events [5, 6, 3]. Stone disease has been estimated to account for up to 1 % of all hospital admissions. Health care costs for kidney stones exceed 2 billion dollars per year in the US health system in 2002 [7], the costs in European countries were proportionally similar or even higher [8]. Complications of (recurrent) stone disease include pain, urinary tract infections, loss of renal function, and highly recurrent forms may cause end stage kidney disease with the need for renal replacement therapy [9, 10].

Kidney stone disease is multifactorial with a strong genetic component and important contributions from environmental factors. The genetic basis of kidney stone disease is evident from the highly increased risk to develop kidney stones in patients with a positive family history and from twin studies. Patients with a positive family history have a 2-3 times higher risk to develop stones [11]. Likewise, studies in twins suggested a 50-60 % heritability for the risk of kidney stones with a higher risk for men than women [12, 13]. More recently, genome wide association studies as well as studies examining the heritability of kidney traits involved in kidney stone disease such as uric acid metabolism or tubular transport processes have identified a high heritability of these functions and identified multiple genetic loci associating with metabolic functions and/or risk to develop kidney stones [14-18].

Dietary habits are the most important environmental factor in the pathogenesis of stone disease. In fact, analysis of the NHANES cohorts suggested that only 5 factors may explain up to 50 % of the risk to develop kidney stones, namely BMI, fluid intake, DASH-like diet, calcium intake and sugar containing beverages [19]. These 5 factors are all potentially modifiable. However, dietary habits often vary between countries and populations and the impact of diets on stone risk may depend to some extent on underlying genetic risk factors. The interactions between genetics and diet in kidney stone disease are complex. Interestingly, recent data suggest a strong heritable component in dietary traits associated with nephrolithiasis, indicating that the separation between dietary and genetic risk factors of nephrolithiasis may be less distinct than previously appreciated [20].

Little is known about the epidemiology of kidney stone disease in Switzerland. However, Switzerland with different language regions, different influences from neigbouring countries with the same language (Italy, France, Germany and Austria) and thus various dietary habits within these regions provides an ideal setting to study the impact of diet on kidney stone disease. The Swiss Kidney Stone Cohort (SKSC) addresses several questions central to a better understanding of kidney disease in Switzerland and beyond.

The aims of the SKSC are: 1) to provide data on kidney stone disease in the Swiss population, 2) to study genetic and environmental factors contributing to stone disease and their interactions, 3) to study longitudinally the course of stone disease, and 4) to provide biosamples for further studies.

Study design and protocol

The Swiss Kidney Stone Cohort (SKSC) is an investigator-initiated prospective, multi-centric longitudinal, observational study in patients with kidney stones followed over a period of 3 years after inclusion. The study has been registered on ClinicalTrials.gov (NCT01990027) and is performed according to the current version of the declaration of Helsinki, ICH-GCP, GEP, and Swiss law on human studies. In particular, SKSC has been approved by the Swiss cantonal ethics committees. SKSC encompasses 782 patients with kidney stones. It also includes a smaller cohort of 207 healthy controls proven by abdominal CT to be stone-free. However, healthy controls were studied only at baseline and without follow-up visits. The study has been performed at six sites in Switzerland: Aarau, Basel, Berne, Geneva, Lausanne, and Zurich. Biobanking of DNA, urine and blood samples allows for further analyses.

Inclusion and exclusion criteria

We recruited patients with kidney stones that fulfilled the following criteria

Inclusion criteria:

- Signed declaration of informed consent
- Age ≥ 18 yrs
- Recurrent kidney stone episodes (more than 1) or an individual kidney stone episode with at least one of the following risk factors:
    - The first manifestation before age of 25 yrs
    - Positive family history
    - Non-calcium oxalate stones
    - Gastrointestinal disorders (e.g. gastric bypass surgery, inflammatory bowel disease, malabsorption etc.)
    - Osteoporosis
    - Nephrocalcinosis
    - Single kidney
    - Current pregnancy
    - Gout
    - Metabolic syndrome (including diabetes mellitus type 1 and 2)
    - Residual calculi (at least 3 months after the therapy)
    - Bilateral or multiple stones
    - Chronic urinary tract infection
    - Chronic kidney disease (eGFR < 60 ml/min)
    - Kidney transplant

Exclusion criteria:

- No signed informed consent form
- Age <18 yrs
- Inability to follow the protocol

For the healthy control group, the following inclusion and exclusion criteria were set:

Inclusion criteria:

- Signed declaration of informed consent
- Male or female
- No signs of kidney-stone evaluated by medical history and stone-free low-dose CT-scan
- Age ≥ 18 yrs

Exclusion criteria:

- No signed informed consent form
- Age < 18 yrs
- Pregnancy
- History of kidney stones
- Low-dose CT-scan positive for kidney stones or calcification during screening phase
- Not fulfilling inclusion criteria

Patients were mostly referred by departments of urology of the same or affiliated hospitals. Healthy control subjects were recruited either from former participants of the SKIPOGH study [21] where potential participants were contacted taking into consideration their age, sex, absence of stone disease in medical history, and whether they had been previously found to be free of kidney stones by ultrasound. Since SKIPOGH is a family-based cohort that is based in Geneva, Lausanne and Berne, only one member of each family was contacted to test for further eligibility based on inclusion and exclusion criteria. In order to match participants recruited in Zurich, additional participants of the control cohort were recruited by open advertisements and screened at the University Hospital Zurich.
Recruitment started in April 2014 and the last patient was enrolled on March 30, 2020. The last 3-year follow-up visits (V7) are scheduled for spring 2023.

Study visits
Patients with stone disease are followed over 3 years with regular visits (V1-7) to collect clinical information, urine and blood samples (table 1). At each visit (except for visit 4 at 3 months), participants complete two consecutive 24 hr dietary recalls, in which they describe and quantify every food and beverage consumed over the 48 hr recall period (see below: diet assessment). Patients with stone disease have a total of 7 visits during the 3 years:

Screening visit (V1)
Patients with stone disease and a recent stone episode are screened for eligibility and are given information to obtain informed consent. The last stone episode should have been at least 4 weeks prior to the visit but not longer than 3 months ago. Patients are physically examined and patient and family history data are collected through a structured interview.
Patients are instructed for 24 hr urine collections and collectors are dispensed. Also forms for food frequency questionnaires (FFQ) and physical activity frequency questionnaires (PAFQ) are provided.

Visit 2 (2 weeks follow-up)
Only patients with signed informed consents are seen. V2 should take place within 2 weeks after V1. Blood and morning spot urine samples are collected from overnight fasted patients, the containers from the two subsequent 24 hr urine collections and FFP and PAFQ forms are returned. Physical parameters are documented. Spot urine samples are immediately analyzed for pH and crystalluria. A detailed and standardized food recall interview is conducted by a trained dietician covering the two days of the two 24 hr urine collections.

Visit 3 (4 weeks follow-up)
Visit 3 takes place within 2 weeks after visit 2. Patients receive feedback on their results from urine and blood analysis (V2). Patients may receive dietary counseling or drug therapy based on their individual findings. Patients receive the urine sample containerr for the next collections.

Visit 4 (3 months follow-up)
Visit 4 follows up on therapeutic measures initiated during visit 3 and is planned three months after visit 3. Detailed anamnesis, physical examination, inspection of the dietary diaries, and analysis of morning urine, a single 24hr urine collection and blood are included. A structured 24hr recall interview on diets consumed during 24hr urine collection is done by trained dieticians.

Visit 5 (1 year follow-up) and annual follow-ups (V6-V7)
Visits 5 – 7 take place 1, 2 and 3 years, respectively, after visit 3 and serve to further follow up on the effect of therapeutic measures and to record data and collect samples on the longitudinal course of disease. V5 consists of two actual appointments about 2 weeks apart. During the second appointment, results from blood and urine analysis are discussed with patients and if indicated therapeutic measures adjusted. Otherwise, V5-7 are conducted in the same manner as visit 2.

After V7 – follow-up until year 10
After the end of the 3-year period and after completing visit 7, biannual structured interviews by phone are conducted to collect data on further stone episodes, other medical events, and current drug intake. Phone interviews are planned until 10 years after recruitment. The following data will be recorded: kidney stone events

and associated complications, type of stone (if known), urological interventions, cardiovascular disease and events, newly diagnosed diabetes, hypercholesterolemia, hypertension, smoking status, current medications, body weight, dietary habits (with particular emphasis on consumption of salt, dairy products, meat, beverages, and special dietary requirements), any other health-related event (e.g. pregnancy, surgery, etc.).

Control cohort – visits

Individuals participating in the control cohort complete a screening visit and V1 and V2 like patients with stone disease (table 2). Unlike stone patients, a low dose CT is performed during the screening visit to exclude asymptomatic stone disease or other kidney calcifications. Low-dose CT allows to detect kidney stones or calcifications with a high sensitivity of nearly 98% and specificity of 97% [22]. Radiation exposure is in the range of 0,5-1,9 mSv. Only individuals completely free of kidney stones or calcifications visible in the low dose CT are included and complete V1 and V2.

Data and sample collection and analysis

Clinical and anthropomorphic data as well as patient history are collected during visits V1-V7. The data includes birth date, sex, BMI, systolic and diastolic blood pressure, history of urinary tract infections, inflammatory bowel disease, abdominal surgery, information of dietary requirements and habits (see below dietary assessment), diabetes, gout, current medications, age of first kidney stone and family history.

Kidney stone composition, recurrence of stones, and urological treatments (i.e. extracorporeal shock wave lithotripsy, ureteroscopy, etc) are recorded.

During visits V2 to V7, the following samples are collected for immediate analysis and biobanking. Biochemical analysis of urine and blood samples has been done in a single centralized laboratory, initially Bioanalytica, in Lucerne, Switzerland and, since May 15, 2017, in the Department of Clinical Chemistry at the Inselspital Berne.

Urine: Two consecutive 24 hr urine collections preceeding the visit day, the first collection is under oil and contains the preservative thymol, the second is collected as native urine. Both urine samples are analyzed for biochemical parameters and urine aliquots are frozen either untreated, alkalinized (with addition of NaOH to pH 8) or acidified (with HCl to pH 2).

Both 24 hr urine samples have been analyzed for urine volume, content of Na^+, K^+, Cl^-, Ca^{2+}, phosphorus, Mg^{2+}, total protein, albumin, oxalate, citrate, creatinine, uric acid, urea, ammonium, pH, and sulfate.

Morning spot urine: Second morning urine is collected, pH measured, and microscopy for crystalluria and urine sediments is performed: 3 fields are examined at 400x magnification on a Türk hemocytometer and representative pictures are taken.

Samples from the second fresh morning urine are kept for biobanking and immediately frozen either as native urine or as acidified/alkalinized urine (urine pH 2 or 8, respectively).

Blood: Samples are taken from fasting (> 6 hrs) patients. Plasma and serum are prepared and frozen for biobanking.

Blood has been analyzed for Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, HCO_3^-, albumin, phosphate, glucose, creatinine, urea, uric acid, parathyroid hormone, calcidiol (25-OH-vitamin D_3), calcitriol (1,25-OH_2-vitamin D_3), HbA1c, and lipids.

For some but not all patients also blood gas analysis was performed yielding pH and HCO_3^-.

During visit 2, EDTA blood was collected for DNA extraction.

Dietary assessment

During V2-V7 data are collected on dietary habits and physical activity using food frequency questionnaires (FFQ) and physical activity frequency questionnaire (FAPQ) [23].

A detailed and structured 48 hr recall interview for food consumed during this period is conducted during visits 2 and 4-7 by trained dietician using a dedicated and validated software to collect the data, GloboDiet® (GD, formerly EPIC-Soft®, version CH-2016.4.10, International Agency for Research on Cancer (IARC), Lyon, France, adapted to the Swiss food market)) [24-26]. The interviews are organized in standardized steps with probes from

the interviewer to help participants remembering food and beverages consumed. In addition, participants conducted a food diary over 48 hrs (V2, V5-V7) or 24 hr (V4) to support the recall.
In GD, a food or beverage is categorized into 18 main food groups (e.g vegetables, cereals, meat, fish and seafood, non-alcoholic beverages). These food groups are divided further into several subgroups. Specific descriptors allow a highly standardized description of foods and recipes [25, 27]. Furthermore, a photobook, also including typical Swiss recipes, helped participants to quantify the amounts of foods and beverages consumed [28].
Also, special dietary habits or requirements such vegetarianism, veganism, or lactose intolerance as well as food supplements (e.g. vitamins, minerals, proteins etc) are specifically recorded.

Further tests

Some centers but not all, perform additional tests such as blood gas analysis, pulse wave velocity measurements at baseline and V7. Results from these tests are also included into the central data base.

Biobanking and centralized data storage

Serum, plasma, and the different urine samples are stored in aliquots at -80 °C in a centralized biobank at the Institute of Physiology, University of Zurich. Freezers are connected to a central alarm to monitor temperature changes.
Likewise, all clinical and biochemical data are stored centrally at the University of Zurich. Data from dietary assessments are stored at UniSanté, Lausanne, Switzerland.

Management of study

SKSC is led by O. Bonny and C.A. Wagner. All centers have two principal investigators. A steering board consisting of representatives of each center plus the two leaders of SKSC and one representative of the Swiss Society of Urology determines strategies and decides on the use of data and biobank samples within SKSC and by external collaborators.

Discussion

Kidney stone disease is a frequent disorder affecting a substantial proportion of the population at least once during their lifetime. In many patients the disease is recurrent and may cause pain, urinary tract infections, and sometimes even loss of renal function. The socio-economic burden of kidney stones is often underestimated but contributes heavily to overall health costs. Thus, better prevention and therapy are urgently needed.

The complex and diverse etiology of kidney stone disease with genetic and environmental risk factors makes diagnosis of underlying causes, effective therapy and prevention often challenging.

SKSC is a prospective multicentric longitudinal observational study to examine causes and consequences of kidney stone disease in the Swiss population. Nearly 800 patients with stone disease and more than 200 proven stone-free control subjects have been recruited. Detailed information on renal function, dietary habits and actual food intake are available. Genetic data from whole exome sequencing are currently obtained and may in future be completed by SNP-chip and/or whole genome sequencing. A major strength of SKSC is the longitudinal follow-up with the collection of detailed biochemical and dietary information. Presently, we plan to follow patients for up to 10 years, the first 3 years with regular visits, biochemical analysis of urine and blood, and biobanking. Thereafter, structured interviews by phone will provide important follow-up information. This approach provides an inexpensive but very valuable information on the long-term outcomes. To the best of our knowledge, this makes SKSC an unique cohort as most other cohorts in this field are rather retrospective or based on a single center.

The importance of diet for kidney stone disease has been known for a long time and been confirmed in various cohorts such as NHANES and others [29, 30, 19, 31, 32]. However, in these cohorts, information on diet is mostly derived from food frequency questionnaire or other forms of retrospective interviews [33]. Most food questionnaires assess dietary intake only for groups of nutrients (i.e. proteins, fat, carbohydrates) or the frequency or size of meals. In contrast, Globodiet interviews gather very detailed information on meal frequency, size, and notably on every single item consumed even considering specific brands of the same food item in a manner adapted to the national food market. This highly detailed information is collected in direct 24 hr recall interviews by trained dieticians using a structured questionnaire [34]. Consequently, this data is crossed with information on the specific composition of nutrients from Swiss food composition tables detailing the content of macro- and micronutrients as either directly measured or provided by suppliers. Based on this data ingested amounts of nutrients can be precisely calculated and in the case of SKSC even be compared to biochemical data in urine and blood collected over the same period of time. In Switzerland, Globodiet and Swiss food composition tables have been used for the nation-wide survey Menu.CH processing information from nearly 2000 Swiss on their dietary habits [35].

Limitations of the study may be the lack of follow-up in the control cohort, the lack of imaging data within the cohort (determining the extent of residual kidney stones or calcification), or the absence of data on gut or urine microbiome.

In summary, SKSC is an investigator-initiated, prospective, multicentric, observational, longitudinal study to examine causes and course of kidney stone disease in the Swiss population. A major asset of this cohort is the long follow-up, the deep phenotype with rich data on dietary intake and biochemical data from urine and blood and the associated biobank allowing for further analyses. SKSC is open to collaborations at the national and international level.

Ethical approval
The Swiss Kidney Stone Cohort has been approved the cantonal Swiss Ethics committees from all centers involved under the numbers KEK-ZH-Nr. 2013-0330 and BASEC: PB_2016-01578. SKSC adheres to declaration of Helsinki, ICH-GCP, GEP, and the Swiss law on human studies.

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Conflicts of Interest
HS has served on advisory boards for Alnylam. AR received support for attending meetings and travel expenses by Salmon Pharma GmbH. CAW has received honoraria from Salmon Pharma GmbH, Medice, Kyowa Kirin, Advicenne, and Chugai.

Authors contribution
All authors contributed to the development of the study protocol, NM wrote the study protocol, CAW drafted the manuscript. All authors contributed to patient recruitment and/or management of the cohort. All authors approved the study protocol and manuscript.

Data statement
All data are accessible upon request to authors.

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Table 1: Patients with kidney stone disease

Visit number	V1 Screen	V2 + 2 weeks	V3 + 4 weeks	V4 + 3 months	V5-V7 yearly	V8-V10 Phone, biannually
Time point +/- tolerance	≥ 4 weeks post stone passage or intervention	V1 + 2 weeks ± 2 weeks	V2 + 2 weeks ± 2 weeks	V2 + 3 months ± 4 weeks	V2 + 12 months ± 1 month	V2 + 60 months etc. ± 1 month
Who	physician	Study nurse, dietician	physician	physician + study nurse, dietician	physician + study nurse, dietician	physician + study nurse
Informed consent explained and signed	√	√				
Inclusion/exclusion criteria	√	√				
Demographic parameters	√	√		√	√	
Medical history	√	√		√	√	
Physical examination	√	√		√	√	
Instruction for 24h urine collection	√					
Food diary		√		√	√	
Food Frequency Questionnaire (FFQ)		√		√	√	
Physical activity frequency questionnaire (PAFQ)		√		√	√	
Standardized 48 hr food recall interview		√		√ (24h)	√	
Pulse wave velocity (optional)		√			Only at V7	
Urine analysis		√		√	√	
Urine microscopy		√		√	√	
Blood analysis		√		√	√	
Urine and blood for biobanking		√		√	√	
EDTA blood for DNA extraction		√				
Discussion of results and initiation of therapies			√	√	√	

Table 2: Healthy control subjects

Visit no	Screening	V1	V2
Time point	**before V1&V2**		Within 2 weeks after V1
Who	physician	physician	Study nurse, dietician
Informed consent explained and signed	√	√	
Inclusion/exclusion criteria	√	√	
Demographic parameters		√	
Medical history		√	
Physical examination		√	
Instruction for 24h urine collection		√	
Food diary			√
Food Frequency Questionnaire (FFQ)			√
Physical activity frequency questionnaire			√
Standardized 48 hr food recall interview			√
Urine analysis			√
Urine microscopy			√
Blood analysis			√
Urine and blood for biobank			√
EDTA blood for DNA			√
Imaging (low-dose CT)	√		