Journal of Nephrology (2019) 32:681–698
https://doi.org/10.1007/s40620-019-00587-1

COMMENTARY

Meeting report of the "Symposium on kidney stones and mineral metabolism: calcium kidney stones in 2017"

Agnieszka Pozdzik[1,2] · Naim Maalouf[3] · Emmanuel Letavernier[4,5] · Isabelle Brocheriou[6,7] · Jean-Jacques Body[8] · Benjamin Vervaet[9] · Carl Van Haute[10] · Johanna Noels[10] · Romy Gadisseur[11] · Vincent Castiglione[11] · Frédéric Cotton[12] · Giovanni Gambaro[13] · Michel Daudon[4,5] · Khashayar Sakhaee[3]

Received: 3 October 2018 / Accepted: 16 January 2019 / Published online: 24 January 2019

Abstract

A symposium on kidney stones and mineral metabolism held on December 2017 in Brussels, Belgium was the first international multidisciplinary conference of the International Collaborative Network on Kidney Stones and Mineral Metabolism. This meeting addressed epidemiology, underlying pathophysiological mechanisms, genetics, pathological, as well as clinical and research topics. The participants included clinicians and recognized experts in the field from Europe and the United States interacted closely during the symposium which promoted a chance to explore new frontiers in the field of kidney stone disease. This manuscript summarizes some of the major highlights of the meeting.

Keywords Kidney stones · Nephrocalcinosis · Nephrolithiasis · Chronic kidney disease · Hypercalcemia · Hypercalciuria · Hyperoxaluria

Abbreviations

CaOx	Calcium oxalate
CKD	Chronic kidney disease
CN	Crystalline nephropathy
ESKD	End-stage kidney disease
FTIR	Fourier transform infrared spectroscopy
ICNKSMM	International Collaborative Network on Kidney Stones and Mineral Metabolism
KSF	Kidney stones formers
KSD	Kidney stones disease
UA	Uric acid
XRD	X-ray diffraction

✉ Agnieszka Pozdzik
Agnieszka.Pozdzik@chu-brugmann.be

1 Kidney Stones Clinic, Nephrology and Dialysis Clinic, Centre Hospitalier Universitaire, Brugmann Hospital, Brussels, Belgium

2 Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium

3 Department of Internal Medicine, and Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, USA

4 Service des explorations fonctionnelles multidisciplinaires, Tenon Hospital, AP_HP, Paris, France

5 INSERM UMRS 1155, Université Pierre et Marie Curie-Paris VI-Sorbonne Universités, Paris, France

6 Department of Pathology, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France

7 INSERM Unit U1155, Paris, France

8 Department of Internal Medicine, Brugmann Hospital, Centre Hospitalier Universitaire, Université Libre de Bruxelles (ULB), Brussels, Belgium

9 Laboratory of Pathophysiology, Antwerp University, Antwerp, Belgium

10 Department of Urology, Brugmann Hospital, Centre Hospitalier Universitaire, Université Libre de Bruxelles (ULB), Brussels, Belgium

11 Department of Clinical Chemistry, EuSpLM, Laboratories "Emergency, Allergy, Urolithiasis", University Hospital of Liège, Liège, Belgium

12 Department of Clinical Chemistry, LHUB-ULB, Brussels, Belgium

13 Division of Nephrology and Dialysis, Gemelli University hospital, Rome, Italy

Introduction

Kidney stone disease (KSD) is a common disorder of mineral metabolism worldwide [1]. Its prevalence is rising, causing significant morbidity with a considerable economic impact, in particular among older adults compared to younger adults [2–4]. According to the latest estimate from 2007 to 2010 from the National Health and Nutrition Examination Survey (NHANES), the overall prevalence of kidney stones (KS) in the United States was 10.6% in men and 7.1% in women [5]. Therefore, 1 in 11 individuals in the United States had a history of kidney stones, in contrast to the previous estimate of 1 in 20 in the United States population from the late 1980s [5]. A similar rise in prevalence was detected in many European countries [6, 7].

Conditions associated with metabolic syndrome are risk factors for KS formation in general, and uric acid stones in particular [5, 8–10]. However, calcium-based stones remain by far the most commonly encountered KS [8, 10, 11], and hypercalciuria is the most frequently identified metabolic abnormality in calcium stone formers [9, 12].

In recent years, KS has emerged as a multi-systemic disorder. In general, kidney stone formers independent of their stone composition have twice the risk of CKD compared to non-stone formers [13–15]. Nephrolithiasis can impair kidney function with complications such as obstruction, infection, or secondary to urological procedures, or may be primary in nature with parenchymal damage induced by the underlying conditions leading to stone formation such as monogenic disorders, nephrocalcinosis, and primary and secondary hyperoxaluria [16].

The International Collaborative Network on Kidney Stones and Mineral Metabolism (ICNKSMM) held in Belgium in December 2017 (http://www.chu-brugmann.be/en/news/20171207-kidneystones.asp) bridged together practitioners and academicians in the field to develop a common program dedicated to understanding the underlying pathophysiologic mechanisms, genetics, as well as diagnosis and management of the population of stone formers. Another major goal of the Symposium was to cultivate interest among young physicians to engage in kidney stone research in the future.

Genetics of nephrocalcinosis and nephrolithiasis

The etiology of the most frequent forms of calcium stones nephrolithiasis is multifactorial; involving nutritional, environmental, and polygenic genetic determinants according to Prof Giovanni Gambaro from Nephrology and Dialysis Division, Gemelli University Hospital from Italy. Nephrolithiasis is a common condition, and genetics play a central role in defining the metabolic "milieu" from which KS may form [17–19]. There is a clustering of KS in nearly 50% of KSF families. Family history of KSD is significantly associated with more complex presentation and higher recurrence rate in idiopathic calcium KSF [20].

KS are frequently associated with urinary metabolic disorders including as hypercalciuria (40 to 75%), hyperoxaluria (5 to 20%), hyperuricosuria (~ 10%) and hypocitraturia (20%). Idiopathic hypercalciuria and calcium stone disease is indeed a complex (multifactorial and polygenic) [21] condition resulting from dietary – environmental interactions in a genetically predisposed subject. Heritability and environment effects have been reported in 56% and 44% respectively [17]. Genome wide association studies (GWAS) in Iceland and Japan have found 8 genes that modulate the risk but are not necessarily directly responsible for KSD [22, 23]. Mendelian disorders causing renal stones and nephrocalcinosis involve mutations in the genes of the calcium sensing receptor, soluble adenylyl cyclase, vitamin D receptor, claudins, chloride channels, sodium/phosphate transporter, carriers involved in the pathogenesis of distal renal tubular acidosis, genes involved in renal morphogenesis, and medullary sponge kidney, as well as many others (Table 1, adapted from [24–27]) [28].

Recent genetic studies led by a single group using exon sequencing of selected gene panels and whole exome sequencing suggested that monogenic disorders may be more common than previously suspected in kidney stone disease [29–31]. In fact, 14 monogenic genes caused nearly 15% of kidney stones in a population of 26 consecutive recurrent KSF [29]. However Prof Gambaro emphasized the high number of pediatric cases and the potential for some selection bias in these studies.

In patients with primary hyperoxaluria in whom no mutation is identified in the coding regions of the three known genes responsible for primary hyperoxaluria (types 1, 2, and 3), testing for mutations in non-coding regions (promoter, introns) or in other gene encoding proteins of oxalate metabolism has been suggested in the further explorations of phenotype-genotype relationships [32]. Diagnosing genetic forms of nephrolithiasis is crucial for personalized medicine in stone formers [33].

Table 1 Monogenic disorders associated with calcium kidney stones and nephrocalcinosis

Disorder	Gene	Protein	Inheritance mode	Clinical manifestation
dRTA autosomal recessive	*ATP6N1B/7q33-q34*	B-subunit ATP6N1Bof the H^+-pump	AR	Defect of the H^+ secretion affecting the α-intercalated cells of the collecting duct Hypokalemic hyperchloremic acidosis with NC and NL
dRTA autosomal dominant	*SLC4A1/17q21-q22*	Anion exchanger (AE1)	AD	Defect in HCO_3^- transport at the basolateral membrane of the α-intercalated cells of the collecting duct. Hypokalemic hyperchloremic acidosis, NC and NL
dRTA with neural deafness at birth or late onset	*ATP6B1/2cen-q13*	Subunit ATP6B1 of the H^+-pump	AR	Defect of the H^+ secretion in the α-intercalated cells of the collecting duct. Hypokalemic hyperchloremic acidosis with NC and NL, and neural deafness
Bartter's syndrome type 1	*NKCC2/15q15-q21.1*	NKCC2 sodium–potasium–chloride transporter	AR	Decreased Na^+, K^+, and Cl^- reabsorption in the ascending limb of Henle loop leading to hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism, and in some cases NC
Bartter's syndrome type 2	*KCNJ1/11q24*	ROMK1 potassium channel	AR	Decreased Na^+, K^+, and Cl^- reabsorption in the ascending limb of Henle loop leading to hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism, and in some cases NC
Bartter's syndrome type 5 Autosomal dominant hypocalcemias with hyeprcaclciuria hypoparathyroidism (ADHH)	*CASR*/3q13.3-q21	Calcium-sensing receptor (activating mutation)	AD	Inhibition of Ca^{++} reabsorption in the ascending limb of Henle loop leading to hypercalciuria, hypocalcemia, hyperphosphatemia, and hypophosphaturia, and in some cases hypokalemia. NC in some cases Hypocalcemia, hypercalciuria, normal PTH, recurrent NL, and NC, particularly during treatment with vitamin D and calcium supplementation. Children may present with seizures and neuromuscular irritability during periods of stress; low serum magnesium in some cases
Familial hypomagnesemia with hypercalciuria and NC (FHHNC)	*CLDN16/3q27*	Claudin 16	AD	Urinary losses of Mg^{++} and Ca^{++} with NC, and progressive kidney failure in homozygotes; heterozygotes may produce kidney stones only
Familial hypomagnesemia with hypercalciuria and NC with ocular impairment	*CLDN19*/1p34.2	Claudin 19	AD	Renal wasting of Mg^{++} and Ca^{++}, NC, and progressive kidney failure in homozygotes; macular colobomata, myopia, and nystagmus

Table 1 (continued)

Disorder	Gene	Protein	Inheritance mode	Clinical manifestation
Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)	*SLC34A3*/ 2c/5q35 (NPT2c)	Sodium-dependent phosphate cotransporter	AR	Renal phosphate wasting, hypophosphatemic rickets, leg bowing, short stature, elevated $1,25(OH)_2D$ levels, hypercalciuria, NC, and kidney stones
Dent's disease (also known as Dent-1)	*CLCN5/Xp11.22*	Chloride channel 5 on the endosome membrane	X-linked recessive	Multiple reabsorption defects in the proximal tubule associated with NL, NC, and in many cases end-stage renal disease (ESKD)
Lowe's syndrome (also known as Dent-2)	*OCRL1/Xq26.1*	Phosphatidylinositol 4,5-bisphosphate 5-phosphatase	X-linked recessive	Multiple reabsorption defects in the proximal tubule (cf. Dent's) NL, NC, and many cases ESKD. Hydrophthalmia, cataract, mental retardation (less common in Dent-2 variant)
Idiopathic infantile hypercalcemia	*CYP24A1*	25-hydroxyvitamin D 24-hydroxylase	AR	Hypercalciuria, hypercalcemia, suppressed parathyroid hormone, high levels of 25-hydroxyvitamin D and of 1,25-dihydroxyvitamin D, NL
Pseudoxanthoma elasticum	*ABCC6/16p13.11*	Multidrug resistance-associated protein 6 (MRP6, also known as the ABCC6 protein)		Low levels of pyrophosphate, NL, Randall's plaque formation, tissue calcification
MacGibbon–Lubinsky syndrome (ERS, enamel-renal syndrome)	*FAM20A/17q24*	Putative kinase in Golgie apparatus	AR	Characteristic dental defects (amelogenesis imperfecta, gingival hyperplasia, impaired tooth eruption) and NC
Primary hyperoxaluria (PH) type 1	*AGXT/ 2q36-37*	Alanine glyoxylate aminotransferase (AGT)	AR	NC NL, renal impairment, and ESKD in ~ 50% of patients by early adulthood. Non-renal manifestations of systemic oxalosis include cardiac conduction defects, bone pain, increased risk of fractures, and diminished visual acuity
Primary hyperoxaluria type 2	*GRHPR/9p11*	Glyoxylate reductase/ hydroxypyruvate reductase	AR	Patients with PH type 2 generally have less severe disease than those with PH type 1. Patients primarily present with recurrent urolithiasis, are less likely to have NC, and rarely progress to ESKD
Primary hyperoxaluria type 3	*HOGA1*	Mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme		Patients with PH type 3 generally present early in life (mean age, 2 years) with NL. In contrast to the other two forms of PH, patients with PH type 3 typically do not have recurrent NL after the age of 6 years, and do not progress to ESKD

Table 1 (continued)

Disorder	Gene	Protein	Inheritance mode	Clinical manifestation
Williams–Beuren Syndrome (WBS)	*ELN 7q11.23 28*	Elastin gene and *LIMK1*		'Elfin' face, supravalvular aortic stenosis, hypertension, impaired cognition, short stature, endocrine, genitourinary, auditory, dental, ophthalmologic, and dermatologic abnormalities. Episodic hypercalcemia and hypercalciuria; NC in 45–10% of patients
Medullary sponge kidney (MSK)	*GDNF and RET*	Glial cell line–derived neurotrophic factor and receptor tyrosine kinase	AD, variable penetrance	Recurrent calcium NL and NC, hypercalciuria, hypocitraturia, and incomplete and overt dRTA (2.9% and up to 40% of patients, respectively), metabolic bone disease. Chronic pain, recurrent episodes of urinary tract obstruction, and infection; however, normal kidney function in the majority of patients with rare reports of ESKD

dRTA distal renal tubular acidosis, *ESKD* end stage renal disease, *NC* nephrocalcinosis, *NL* nephrolithiasis, *PTH* parathyroid hormone, *ROMK* renal outer medullary potassium

Epidemiology, morphoconstitutional classification and its correlates with pathogenesis and epidemiology of kidney stones

The incidence of KSD has progressively increased during the past 30 years in most industrialized countries underlined Prof Michel Daudon, head of the Centre de Recherches et d'Informations Scientifiques et Techniques Appliquées aux Lithiases (Laboratoire CRISTAL) since 1986 and responsible for a National Quality Control Program on Stone Analysis in France since 1990.

Urolithiasis affects between 5 and 12% of the general population and two times more often males than females. However, a trend to a decrease of the male-to-female ratio has been recently reported in some countries. Calcium oxalate (CaOx) stones are the most common urinary calculi, accounting for more than 70% of all stones in large series published from the beginning of the 1980s. However, differences are found in chemical composition and crystalline phases according to the patient's gender: calcium phosphate is more frequent in female (27.1 vs. 9.7% in males, $p < 0.0001$) while CaOx is more frequent in male patients (74.9% vs 57.9% in females, $p < 0.0001$). Stone composition also varies with age in both genders, as a consequence of changes in lithogenic risk factors. For example, uric acid (UA) stones are infrequent in young stone formers and become the prevalent category in oldest patients in relation to the increase of body mass index and of the type 2 diabetes prevalence. By contrast, among CaOx stones, weddellite is more common in younger than in older patients.

Prof Daudon highlighted that physical methods, mainly X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) reliably identify specific forms of nephrolithiasis involving non-calcium components such as cystine, purines or drugs [34, 35]. For calcium stones, these methods provide information on chemical (CaOx and/or calcium phosphate) and crystalline phases, which appears more clinically relevant. However, the same crystalline phase may result from a variety of pathological conditions. Stone analysis combining morphological examination followed by XRD or FTIR analysis of the core, middle layers, and surface of calculi provides a more complete understanding of etiologic diagnosis than compositional analysis alone. Using this morphological method, stones may be classified into 7 types subdivided in 22 subtypes (Table 2 adapted from [36]) [37]. While crystalline phases may point out the main metabolic disorders involved in stone formation, morphological type is highly suggestive for specific lithogenic processes. Thus, whewellite, which is mainly related to hyperoxaluria, may

Table 2 Daudon's morphoconstitutional classification of kidney stones, main characteristics and corresponding etiologies

Type/subtype	Main component	Surface/color	Section/color	Etiological orientation
Ia	Whewellite	Mammillary with frequent umbilication and Randall's plaque indicating papillary origin/Brown	Compact concentric layers with a radiating organization/ Brown	Dietary hyperoxaluria, low diuresis, intermittent moderate hyperoxaluria, Randall's plaque
Ib	Whewellite		Compact, unorganized ± gaps/Brown to dark brown	Stasis, low diuresis, crystalline conversion from weddellite to whewellite
Ic	Whewellite	Mammillary, rough surface without Umbilication/brown to dark brown	Finely granular, poorly organized/Light color, cream to pale yellow–brown	Primary hyperoxalurias (mainly AGXT type 1 mutation)
Id	Whewellite	Budding surface/Light cream to pale yellow–brown, sometimes whitish in children	Compact thin concentric layers/Beige or pale brown	Malformative uropathy, stasis and confined multiple stones
Ie	Whewellite	Smooth/Beige or pale brown homogeneous	Unorganized or loose areas mixed with compact radiating structure/heterogeneous, pale yellow–brown to brown	Enteric hyperoxaluria, inflammatory (Crohn disease), ileal resections, chronic pancreatitis
		Locally budding, mammillary or rough/heterogeneous, pale yellow–brown to brown		
IIa	Weddellite	Spiculated by aggregation of bipyramidal crystals with right angles and sharp edges/Pale yellow–brown	Loose radial crystallization/Pale yellow–brown	Hypercalciuria with high calcium/citrate ratio
IIb	Weddellite		Compact unorganized crystallization/Pale yellow–brown	Hypercalciuria ± hyperoxaluria ± hypocitraturia, stasis, low diuresis
IIc	Weddellite	Spiculated by aggregatation of bipyramidal crystals with blunt angles and ridges/Pale yellow–brown	Unorganized core with a diffuse concentric compact structure at the periphery/Gray-beige to dark yellow–brown	Hypercalciuria + malformative uropathy + stasis and confined multiples stones
		Rough surface/Gray-beige to dark yellow–brown		
IIIa	Uric acids anhydrous	Homogeneous smooth/Orange, sometimes cream, ochre or yellowish	Homogeneous compact, concentric with a radiating organization/Orange	Low urine pH, stasis, prostate hypertrophy, metabolic syndrome, ammoniagenesis defect
IIIb	Uric acid dihydrate ± uric acid anhydrous	Heterogeneous embossed, rough and surface/Heterogeneous from beige to brown-orange	Poorly organized with frequent porous areas/Orange	Insulin resistance, metabolic syndrome, type 2 diabetes, ammoniagenesis defect, low urine pH
IIIc	Urates salts, ammonium hydrogen urate	Homogeneous or slightly heterogeneous rough and locally porous/cream to grayish	Unorganized porous/whitish to grayish	Hyperuricosuria, neutral or alkaline urine pH, urinary tract infection by urea-splitting micro-organisms—cation associated with urate
IIId	Ammonium hydrogen urate	Heterogeneous embossed, rough and porous/Heterogenous grayish to dark brown	Alternated layers, thick and brownish or thin and grayish, locally porous. Sometimes, locally purplish	Chronic diarrhea, electrolytes and alkali loss, high urate concentration in urine, low phosphate intake, laxative abuse

Table 2 (continued)

Type/subtype	Main component	Surface/color	Section/color	Etiological orientation
IVa1	Carbapatite	Rough homogeneous/Whitish to beige	Poorly organized or diffuse concentric layers/Whitish to beige	Hypercalciuria, urinary tract infection see carbonatation rate of carbonated calcium phosphate
IVa2	Carbapatite	Embossed and varnished with small cracks. Glazed appearance/homogeneous, pale brown-yellow to pale brown	Compact alternated layers, thick brown-yellow and thin beige/multiple nuclei (from collecting duct origin)	Inherited or acquired distal renal tubular acidosis, Sjögren syndrome, chronic hepatitis
IVb	Carbapatie + other calcium phosphates (±struvite)	Heterogeneous, both embossed and rough with confluent superficial deposits/Heterogeneous, cream to dark brown	Irregularly alternating thick witish and thin brown-yellow layers	Urinary tract infection, hypercalciuria, primary hyperparathyroidism
IVc	Struvite	Homogenous made of amalgamate crystals with blunt angles and edges/whitish	Crude radial crystallization/Whitish	Urinary tract infection by urea splitting bacteria
IVd	Brushite	Finely rough or dappled/whitish to beige	Radial crystallization with more or less visible concentric layers/Whitish to beige	Hypercalciuria, primary hyperparathyroïdisme, phosphate leak, medullary sponge kidney
Va	Cystine	Rough/Yellowish	Poorly organized, sometimes a radiating organization/Yellowish	Cystinuria
Vb	Cystine	Smooth/Homogeneous, cream to yellowish	Concentric layers at the periphery, an unorganized core/Heterogeneous, cream (periphery) to yellowish (core)	Cystinuria + inadequate diet and/or medical management + stasis
VIa	Proteins	Homogeneous matrix soft calculi/Cream to pale brown	Unorganized/cream to pale brown	Urinary tract infection, chronic pyelonephritis
VIb	Proteins + drugs or metabolic compounds	Heterogeneous, irregularly rough locally scaled/Dark brown to black	Crude and diffuse foliated/Dark brown to black. Other components often present alter the structure and the color	Example of drug-induced stone (mixture of proteins and atanazavir)
VIc	Proteins + whewellite	Homogeneous, smooth with clefts and scales/Dark brown	Dark-brown protein shield surrounding a loose, unorganized light core containing whewellite crystals mixed with proteins	End stage renal failure + relatively high urinary calcium concentration (long term calcium and Vitamin D therapy)
VII	Miscellaneous	Various morphologies and colors according to the stone composition (infrequent purines and drugs)	Variable organization and color according to the stone composition	

present as five different morphologies: among them, type Ia is often related to moderate hyperoxaluria due to low diuresis or intake of oxalate-rich food. By contrast, type Ic is pathognomonic of genetic heavy hyperoxaluria [38] and type Ie is a marker for enteric hyperoxaluria [34]. Sequential analysis may reveal changes with time in the factors involved in stone formation.

Prof Khashayar Sakhaee from the United States underlined the association between changes in kidney stone composition, with the varying demographics and biochemical profiles in a retrospective study in the Unites States from 1980 to 2015 involving 1516 KS patients. This study showed the proportion of UA stones increased from 7 to 14% [8]. The proportion of females with KS increased over time but the increase in females was more significant among calcium stone formers. Age and body mass index increased with time in both UA and calcium stone formers [39, 40]. However, UA stone formers were consistently older and had a higher body mass index and lower urinary pH than calcium stone formers [8]. Hyperuricosuria itself or concomitantly with hypocitraturia, hyperoxaluria and hypercalciuria could lead to hyperuricosuric calcium nephrolithiasis [41]. A separate retrospective study of 2132 KS patients from Europe demonstrated that obese and overweight KSF exhibited higher urinary UA, urinary sodium, urinary calcium and significantly lower urinary pH [9]. In addition to increased prevalence of metabolic syndrome in the past decades, global warming and greater urbanization are predicted to contribute to increased risk of nephrolithiasis in the future [42]. Finally, the protective impact of dietary approaches to KS prevention is more apparent in single stone formers, whereas anti-lithogenic drugs are more effective for recurrent KSF [43].

Cell biology of nephrocalcinosis and nephrolithiasis

Considering the increased incidence of KSD Benjamin Vervaet, cell biology researcher from Belgium presented the interactions between crystals and renal tubular epithelial cells, and the role of the renal tubular epithelium both in the onset and outcome of early stages of KSD. Like any other bio-mineralization process, nephrocalcinosis and nephrolithiasis are manifestations of a complex interplay between crystals physicochemical characteristics and cell biology [44]. This century, it has become clear that nephrocalcinosis and nephrolithiasis are to be considered two independent entities. In depth microscopic and histopathologic research was crucial to differentiate between intratubular and interstitial nephrocalcinosis. On the one hand, intratubular nephrocalcinosis develops as a consequence of phenotypical changes of the renal tubular epithelial cells, which, due to prior injury, gain crystal-binding properties [45]. On the other hand, interstitial nephrocalcinosis starts as a *de novo* crystal formation process in the interstitium and is thought to be the result of local patho-physiological disturbances in proper ion and/or acid-base handling [46]. Both forms of nephrocalcinosis can progress to nephrolithiasis, however only under certain specific conditions. In addition, being evolutionary challenged, the kidney displays several crystallization defense mechanisms. At least in the condition of intratubular nephrocalcinosis, kidney is even capable of actively removing and dissolving retained crystals in a cell-driven process [47]. Although it is clear that the kidney has still not revealed all its cell biological secrets, concerted research actions has led to the development of solid etiological concepts.

Determinants of Randall's plaque formation

The mechanism of heterogeneous nucleation at the tip of the renal papilla that give birth to CaOx stones was detailed by Prof Emanuel Letavernier from Service des explorations fonctionnelles, Tenon Hospital in Paris, France. He underlined that the genetic and environmental determinants of Randall's plaque formation are still partly described.

Indeed, KS were for the first time described to originate from calcium phosphate plaques growing in the interstitial tissue, breaking the urothelium and then promoting monohydrate CaOx crystal aggregation at their contact over 6 decades ago. The development of endoscopic procedures allowing plaque visualization renewed interest in Randall's plaque. In parallel, a dramatic increase in the proportion of CaOx stones grown on Randall's plaque during the past decades has been reported in France [48].

Hypercalciuria is probably a major risk factor for Randall's plaque formation. Increasing sensitivity to vitamin D in KSF presenting with Randall's plaque has been proposed [49, 50]. Calcification inhibitors might be essential to prevent Randall's plaque development [50, 51]. The identification of environmental factors and genetic polymorphisms promoting Randall's plaque formation have emerged as essential to eventually prevent or slow down plaque formation in predisposed children and young adults [52].

Pathology of crystals-induced nephropathy

Sustained exposure of tubular epithelium to crystals induce a lesion classified as crystal induced nephropathy or crystalline nephropathy (CN), term applied to patterns of renal injury sharing the distinctive finding of crystals within tubules and/or interstitium. Crystal nephropathy is not only related to the crystals deposition as detailed Prof Isabelle Brochériou from Pathology Department at Pitié-Salpêtrière

Hospital, Sorbonne Université and INSERM Unit U1155 in Paris, France. Indeed, based on the clinical setting in which they are formed, or on the composition of the crystals, CN is divided into the following 4 categories: (1) CN related to dysproteinemia, (2) drug-induced CN, (3) CN related to calcium deposition, and (4) other metabolic and genetic CN forms.

The dysproteinemia-related CN includes light chain cast nephropathy, also known as myeloma cast nephropathy, which is the most common dysproteinemia-related renal disease [53, 54]. Crystalline nephropathy may develop during the use of drugs (ceftriaxone [55]), sulfadiazine [56], acyclovir [57], triamterene [58], atanazavir [59], and others that are excreted by the kidney (see details in recent review [60]). Calcium crystals CN is characterized by abundant tubular and interstitial deposits of calcium phosphate or CaOx crystals, easily distinguished by their tinctorial properties. Hypercalcemia is the most common condition associated with subsequent nephrocalcinosis. Enteric hyperoxaluria is frequently found in CaOx nephropathy, which can also be seen in severe hereditary enzymatic defects known as the primary hyperoxaluria [61]. Some inherited (cystinosis, 2,8-dihydroxyadenine deficiency, primary hyperoxaluria) or acquired metabolic disorders are responsible for crystalline nephropathies [62–64]. Careful clinical-pathologic correlation with concomitant identification of urine crystals

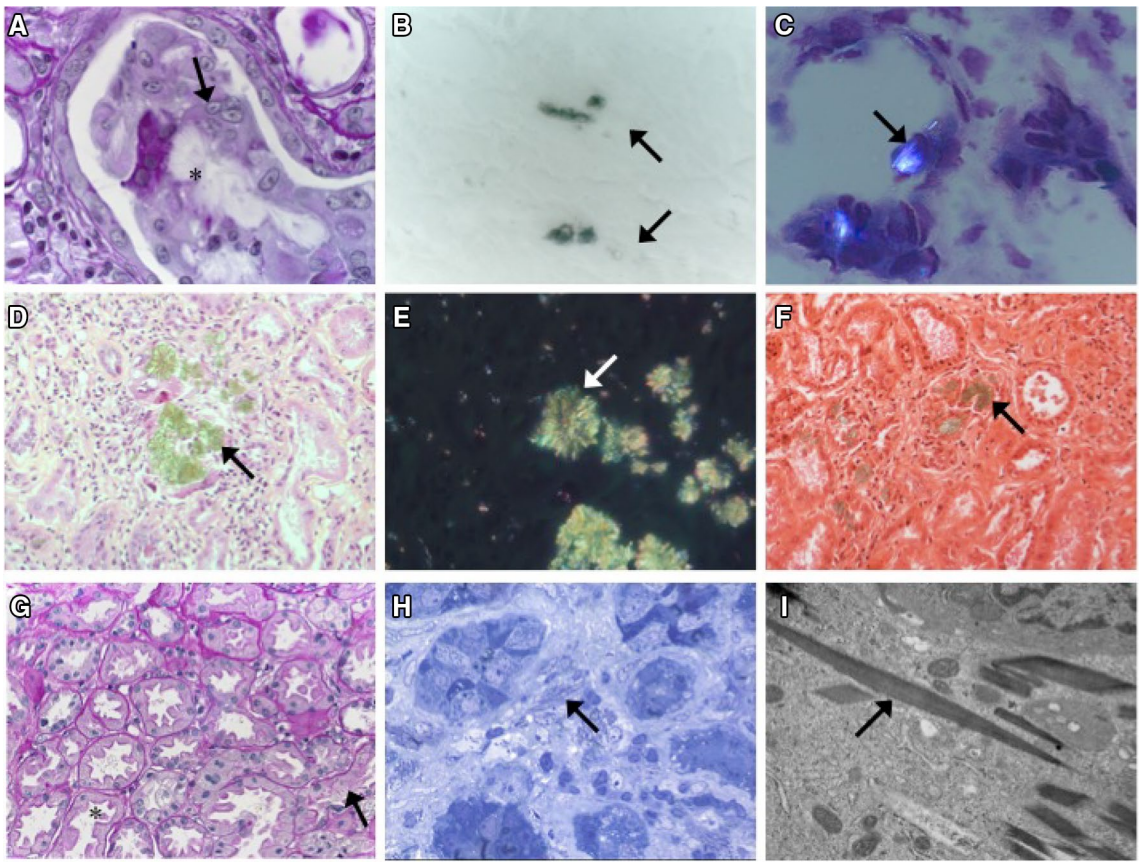

Fig. 1 Representative photomicrographs of crystalline nephropathies. Atazanavir-induced nephropathy: **a** Foreign-body type reaction (arrow) surrounding the crystal (star). PAS staining, original magnification × 200. **b** Cristals (arrows) present on typical frozen section without staining, original magnification × 400. **c** Birefringent, intratubular and intracellular crystals observed under polarized light microscopy analysis, original magnification × 400. Crystalline nephropathy due to 2,8-dihydroxyadeninuria: **d** Several yellow-brownish crystals (arrow) within the cytoplasm of tubular epithelial cells and foreign-body type reaction within interstitium surrounding the crystal aggregates. Hematoxylin & eosin staining, original magnification × 400. **e** Polarized light microscopy showed the crystals to be strongly birefringent, demonstrating a radial orientation with a variable appearance, including needle, ring- and spherically-shaped aggregates (so-called Maltese cross pattern was not observed in this case). Original magnification × 400. **f** Crystals are negatives on Van Kossa staining used for identification of calcium deposits, Original magnification × 200. Monoclonal gammopathy of renal significance: **g** Proximal tubular lesions were seen with focal atrophy (star) and brush border disappearance (arrow). PAS staining, original magnification × 200. **h** Crystals were detected in the cytoplasm of interstitial histiocytes (arrow) on toluidine blue staining of semithin sections. **i** Numerous needle-shaped crystals (arrow) in the cytoplasm of altered epithelial cells (crystalline inclusions were observed in the cytoplasm of proximal tubular cells, not shown). Electron microscopy study. Kindly provided by Prof Isabelle Brochériou from Pathology department, Pitié-Salpêtrière hospital, INSERM Unit U1155, Paris, France

(cristalluria) is fundamental in the interpretation of CN etiology [65, 66]. Adequate identification of the causative pathological condition(s) improves the correctness of diagnostic (Fig. 1) allowing a more personalized therapeutic approach that is essential to reduce the risk of kidney function decline [62, 64, 66].

Kidney stones as a multi-systemic illness

If uncontrolled, CN leads to progressive loss of glomerular filtration rate and development chronic kidney disease (CKD). This long-term complication of KSD was presented by Prof Agnieszka Pozdzik from Kidney Stone Clinic, Nephrology and dialysis clinic at Hospital Brugmann, Université Libre de Bruxelles in Brussels, Belgium.

Considering that CKD has become a global public health problem with serious social and economic effects from premature morbidity to death, nephrologists are attentive to identify all possibly treatable CKD risk factors, and KSD is one of them [67].

Indeed, growing evidence demonstrates a consistent relationship between nephrolithiasis and the development of CKD, and leading to end-stage renal disease (ESKD) in more than 3% of cases [68–70]. Moreover, recent epidemiological studies have shown the association of KSD with cardio-vascular disorders, arterial hypertension, obesity, diabetes mellitus, metabolic syndrome that are well-recognized risk factors for CKD (Fig. 2) [71]. Regardless of the associated co-morbid conditions, KSD has been shown to be an independent risk factor in the development of CKD [15]. Definitely, KSF have nearly twice-risk to develop CKD compared with patients without stones. Urolithiasis and its complications or conditions associated with kidney stones have been reported in 5.1% of all ESKD cases [72].

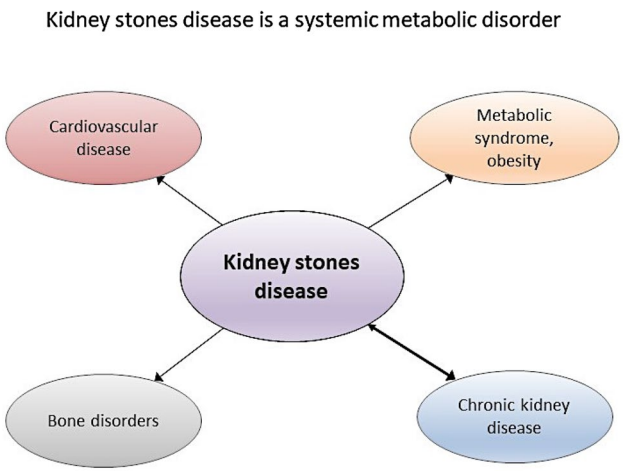

Fig. 2 Interrelationships between kidney stones disease, cardiovascular disease, systemic metabolic disorders, bone metabolism and chronic kidney disease

Other risk factors associated with CKD identified in KSF include: existing kidney functional impairment, recurrent urinary tract infections with kidney stones of particular compositions including struvite, UA stones, symptomatic stones, solitary kidney, neurogenic bladder, renal or urinary tract malformations and ileal diversion, malabsorptive bowel conditions and some monogenic diseases responsible for nephrolithiasis and/or nephrocalcinosis, especially in children (Table 1) [73].

Given the risk of KS recurrence, high morbidity, the necessity of endo-urological or surgical interventions, early diagnosis and specialized management of KSD is indicated [74]. Awareness is essential to rapidly identify the pro-lithogenic metabolic abnormalities, assess the coexistence of renal and/or cardiovascular complications with the aim of controlling KSD and slowing down the CKD progression with adequate treatment [75, 76]. At the present time the evaluation of the global risk of developing CKD/ESKD and of related metabolic disorders during the workup of patients with KS is mandatory (Fig. 3). In addition, the ultrasound scans exploration of KS and related complications such as obstructive nephropathy or urinary tract infection need to be adapted case by case during the follow [77].

Calcium metabolism and kidney stones

In their presentations, Dr. Naim Maalouf and Dr. Khashayar Sakhaee from the Department of Internal Medicine and the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research at the University of Texas Southwestern Medical Center, in Dallas, Texas, USA, reviewed normal calcium homeostatic mechanisms and pathophysiologic mechanisms underlying hypercalciuria. Intrinsic determinants of urinary calcium excretion include factors that impact the filtered load of calcium (via intestinal calcium absorption and bone formation/ resorption), and others that alter renal calcium handling at various segments of the nephron. Extrinsic factors that alter calcium handling involve dietary and other lifestyle factors (including intake of calcium, sodium, animal proteins, etc..), and medications that impact calcium metabolism and ultimately the risk of nephrolithiasis.

Calcium KSD is the second most prevalent kidney disease after arterial hypertension. Approximately 80% of calcium kidney stones are CaOx, with a small percentage (15%) of calcium phosphate. The pathophysiologic mechanisms for calcium KS are complex and diverse [78, 79]. However, both hypercalciuria and hyperoxaluria play a major role in the formation of calcium oxalate stones. Hypercalciuria is a heterogeneous disorder and is commonly due to enhanced

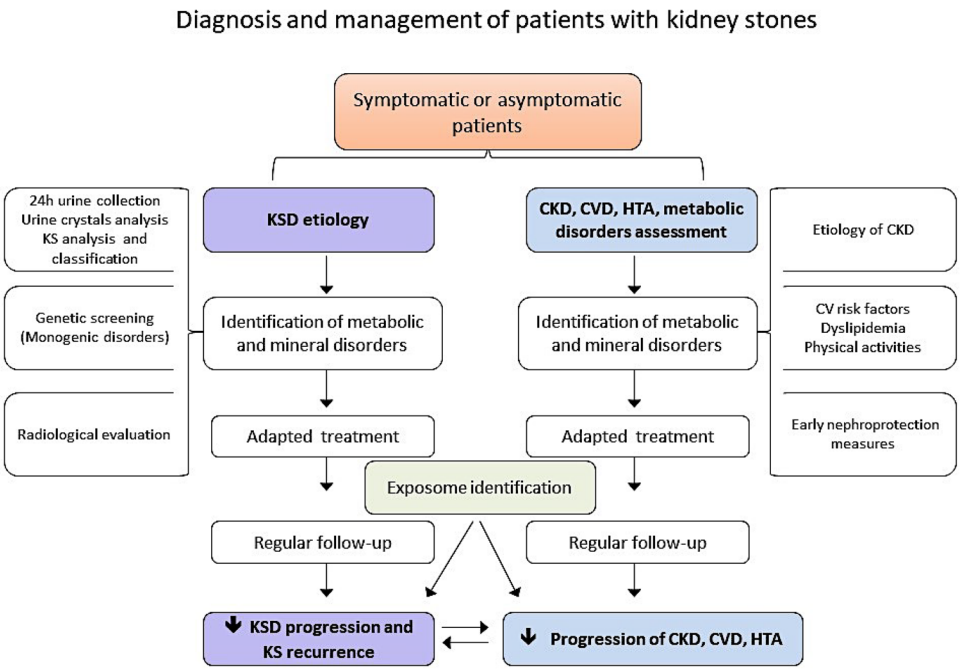

Fig. 3 Proposed evaluations for diagnosis and management of patients with kidney stones. *CKD* chronic kidney disease, *HTA* arterial hypertension, *KS* kidney stone, *KSD* kidney stone disease

intestinal calcium absorption which has been demonstrated to be $1,25(OH)_2$ vitamin D-dependent or independent [80]. A previous study showed that absorptive hypercalciuria is due to increased production of $1,25(OH)_2D$. However, until recently the underlying mechanism of overproduction of $1,25(OH)_2D$ was not fully elucidated. Recently, loss-of-function mutations in *CYP24A1* in patients with idiopathic infantile hypercalciuric nephrolithiasis has been shown to be a responsible mechanism in a subset of this population [81].

With increasing body mass index over the past 3-½ decades, urinary oxalate excretion has gradually and significantly increased [8]. One important underlying mechanism has been linked to differences in the decreasing prevalence of *Oxalobacter formigenes* (OF) colonization among patients with recurrent calcium stone disease [82]. This gram-negative obligate anaerobe bacterium found in gastrointestinal tracts of humans uses oxalate as its sole source of energy [83]. A metabolic study performed in OF colonized and non-colonized stone formers demonstrated significantly higher urinary oxalate among the non-colonized stone-forming population. In addition, an inverse relationship was detected between the number of stone episodes and OF colonization rate [84]. Improved understanding of this pathogenetic pathway will open the door to the new pharmacological approaches using probiotic therapy with OF, oxalate degrading enzymes, and/or recombinant proteins to upregulate of oxalate secretion into the intestinal lumen. The link between overweight, and obesity with alteration in colonization with OF is in part related to the risk of hyperoxaluria in obese subjects. Another potential mechanism has been attributed to the involvement of inflammatory processes caused by obesity resulting in increasing intestinal permeability and enhanced oxalate absorption.

Calcium stone formers are known to exhibit an exaggerated postprandial rise in urine calcium excretion compared with non-stone-forming subjects, and insulin has been proposed to mediate this difference. However, the rise in urinary calcium associated with euglycemic hyperinsulinemia has shown not to be different between KSF and non-stone-forming controls. Thus, insulin is unlikely to play a role in the pathogenesis of hypercalciuria in this population. Lastly, a short-term study has shown that mechanism(s) other than acid load accounts for hypercalciuria induced by a high protein diet. This study will open new insights into the potential role of aromatic amino acids in regulating calcium sensor in gastrointestinal tract and kidney in the pathogenesis of protein-induced hypercalciuria [85, 86].

Primary hyperparathyroidism: diagnosis and treatment

The prevalence of primary hyperparathyroidism (HPT) varies between 1 and 20/1000 [87] underlined Prof Jean-Jacques Body, from Internal Medicine department at Brugmann Hospital, and head consultant for Bone diseases and endocrinology at Institute Bordet (Cancer Centre at the «Université Libre de Bruxelles», Brussels, Belgium).

HPT is nowadays most often asymptomatic and the diagnosis is made by chance or done during the workup of calcium nephrolithiasis or osteoporosis [88]. The incidence of nephrolithiasis has been considerably lowered

but is still the most frequent complication of HPT (17%) whereas osteoporotic fractures are now present in less than 2% of the cases. Hypercalcemia and an elevated parathyroid hormone (PTH) concentration, or at least a PTH level in the upper part of the normal range, generally point to a diagnosis of HPT. Additional tests include an evaluation of renal function, vitamin D measurement, determination of 24-h urinary calcium and bone densitometry [89].

Besides symptomatic HPT, recent recommendations for surgery include age less than 50, serum calcium at least 1 mg/dL above the upper limit of normal, calculated creatinine clearance < 60 ml/min, 24-h urinary calcium higher than 400 mg/day (or 10 mmol/day), and increased stone risk by biochemical stone risk analysis, presence of nephrolithiasis or nephrocalcinosis, and clinical or confirmed osteoporosis [90, 91]. Parathyroid scintigraphy coupled with computed tomography is the best preoperative localization technique. In the hands of an experienced surgeon, the success rate of elective surgery is 96–99% and the rate of permanent complications is lower than 1–2% [92].

Type 2 diabetes and calcium nephrolithiasis

An increased prevalence of nephrolithiasis reported in patients with type 2 diabetes has been approached by Pr Michel Daudon. Because insulin resistance, characteristic of the metabolic syndrome and type 2 diabetes, results in lower urine pH through impaired kidney ammoniagenesis, and since a low urine pH is the main factor of UA stone formation, it was hypothesized that type 2 diabetes should favor the formation of UA stones [93–96]. An abundant literature has extensively confirmed that around 30 to 40% of type 2 diabetic stone formers produce UA stones. While the prevalence of UA stones was significantly increased in French cohort of diabetic patients, Pr Daudon conversely found a significant decrease in calcium phosphate stones and weddellite stones in such patients [93]. By contrast, the proportion of whewellite calculi was not reduced, which suggests that hyperoxaluria could be another metabolic factor involved in stone formation in type 2 diabetes [97]. In addition, the morphology of whewellite stones suggest highs levels of urinary oxalate. Actually, urinary oxalate excretion was found significantly increased in diabetic patients and it was recently reported that glyoxylate, one of the main precursor of oxalate synthesis, was early increased in blood of type 2 diabetic patients [98, 99]. The proposed link between glyoxylate and type 2 diabetes could be AGXT2, an hepatic enzyme that may be down-regulated by loss of function of HNF4α (hepatic nuclear factor 4α) [100].

Nephrolithiasis from vitamin D and calcium supplementation

Calcium and vitamin D supplements are widely used for the prevention and treatment of osteoporosis. These supplements significantly increase urinary calcium, potentially predisposing to calcium nephrolithiasis said Dr Naim Maalouf. In several observational and randomized prospective studies, including the large Women's Health Initiative randomized clinical trial, supplemental calcium and vitamin D significantly increased the incidence of nephrolithiasis [101]. Calcium supplement type (calcium carbonate vs. calcium citrate), dose, and timing of intake, all appear to influence KS risk. In contrast to calcium supplements, higher dietary calcium intake appears to lower the risk of kidney stone formation in several observational studies [102–104]. The impact of vitamin D supplementation (without calcium) has been studied in small prospective studies and found to be safe for the average KSF with vitamin D deficiency [105]. However, a subset of calcium stone formers may exhibit worsening hypercalciuria upon vitamin D supplementation [106]. In his presentation Dr Maalouf reviewed the epidemiology and pathophysiologic mechanisms by which calcium and vitamin D supplements impacts nephrolithiasis risk, and outlined a framework to employ when considering calcium and/or vitamin D supplementation in nephrolithiasis patients (Table 3).

Calcium oxalate stone morphology and urine biochemistry in malabsorptive bowel diseases

In bowel diseases, a malabsorption syndrome may result from intestinal diseases or frequently from gastric bypass surgery prescribed as treatment of morbid obesity [107]. The prevalence of CaOx stones and the renal prognosis of patients undergoing a bariatric surgery or affected by bowel diseases is a matter of concern nowadays underlined Prof Emmanuel Letavernier. Indeed, low diuresis, resulting from reduced water intake and water loss (diarrhea), is a common risk factor of kidney stones. Patients with colon resection and ileostomy form uric acid stones, attributed to bicarbonate loss in the ileostomy and low urine pH. Patients with malabsorption syndrome and functional colon are affected by calcium oxalate stones due to a heavy urinary concentration in oxalate (enteric hyperoxaluria) [108, 109]. Free fatty acids resulting from malabsorption chelate calcium ions in the intestinal lumen and oxalate ions are therefore no more bound to calcium ions and absorbed through the colonic lumen [110]. Kidney stones

Table 3 Considerations in special populations regarding risks associated with calcium and vitamin D supplementation

Population	Consideration/risk
Menopause, elderly	Impaired intestinal calcium absorption
Achlorhydria, malabsorption	Impaired calcium absorption. Calcium from natural sources are preferred over calcium supplementation. Calcium citrate recommended as calcium supplement given its optimal intestinal bioavailbility and it may slightly increase urinary citrate excretion
Obese	Higher baseline bone mineral density, but also CV risk
Advanced CKD	Vascular calcification with greater calcium supplementation
Genetics/Race	Lower urine calcium in Blacks vs. Whites Risk of hypercalciuria/stones with calcium and/or vitamin D supplementation in idiopathic infantile hypercalcemia (mutations in *CYP24A1, SLC34A1*)
1α hydroxylase over-activity (primary hyperparathyroidism, sarcoidosis, others…)	Risk of hypercalciuria/stones with calcium and/or vitamin D supplementation
"Absorptive hypercalciuria"	Risk of hypercalciuria/stones with calcium and/or vitamin D supplementation

Generally, dietary sources of calcium are preferred over supplemental (tablet) in patients whose calcium intake is below the recommended daily intake. The following additional considerations/risk factors should be considered

resulting from enteric malabsorption are typically made of calcium oxalate monohydrate and have a specific morphology: light brown aspect and poorly organized section (type Ie). This morphology is specifically associated to massive hyperoxaluria and high oxalate/calcium ratio in the urine [34].

Urological management of kidney stones

Nowadays there are three most used surgical procedures in the treatment of urinary stones which are shockwave lithotripsy, ureteroscopy and percutaneous nephrolithotomy.

Extracorporeal shock wave lithotripsy (ESWL) is a minimal invasive treatment based on shockwaves that are focused on a target (the stone). The success rate of ESWL said Dr Johanna Noels from Urology department, University hospital Brugmann in Brussels, Belgium, is influenced by the stone localization and anatomical factors of the kidney and ureter, the hardness of the stone which is estimated by measurement of Hounsfield units (HU) on CT-images, (exception cystine stones with low HU, but very resistant), the stone size and patient factors (obesity) and preference of patients [111].

Ureteroscopy is nowadays a common procedure to treat ureteral and kidney stones said Dr Carl Van Haute from Urology department, University hospital Brugmann in Brussels, Belgium. This minimal invasive endo-urological procedure has several advantages such as high stone-free rate (SFR) with a minimal risk of complications. Indications of ureteroscopy were highlighted. Semi-rigid ureteroscopy is used to treat a ureteral stone, mostly in the middle and lower parts of the ureter, whereas flexible ureteroscopy can be used to treat any ureteral stone, as well as kidney stones (upper, mid and lower pole stones). Stone size, stone location and degree of impaction can influence SFR. Stone composition on the other hand won't affect SFR but will lead to longer operative times.

Whether a stone should be completely dusted to achieve the highest SFR, or fragmented with successive extraction, is still controversial. Complication rate is very low (3.5%) and complications are mostly minor. Severe complications, such as ureteral trauma (0–2%) and urinary sepsis with multi organ failure are rare (0.1%).

Percutaneous nephrolithotomy (PCNL) is the oldest minimal invasive treatment strategy to treat large kidney stones. PCNL can be used to treat large kidney stones (> 10 mm), staghorn stones, infection stones, and large or impacted proximal ureteral stones. In case of a retrograde inaccessible urinary derivation (ileal conduit, neobladder, continent urinary reservoirs, etc.), PCNL is a treatment option for kidney and ureteral stones. Among minimally invasive techniques for kidney stones (ESWL/URS), PCNL has definitively the highest SFR for large stones (> 2 cm).

When performing PCNL, obtaining adequate renal access is the key factor. Different imaging methods are used such as ultrasound, fluoroscopy, CT and endoscopy guidance.

PCNL can be performed in prone or supine position. Both positions have benefits and drawbacks, the choice for either position depends on the surgeon's experience, patient-related factors and stone burden.

Modern PCNL techniques include miniaturization of the surgical devices, aiming at less blood loss, less renal damage, and less pain. Standard, mini, ultra-mini, super-mini, mini-micro and micro techniques have been described, all with varying tract sizes (< 5 french up to > 22 french). Smaller tracts lead to less blood loss, less pain and shorter

hospital stays, but have a negative impact on the operative time.

Complications in PCNL can occur. Infectious complications (10%) and bleeding (7%) are the most frequent. Injury to nearby organs (pleura, liver, spleen, colon, etc...) are rare (1%) and can sometimes need to be conservatively managed.

Epidemiology of urolithiasis in Belgium according to Daudon's morphoconstitutional classification

Increasing evidence underlines that morphoconstitutional (MC) analysis is a clue to the pathogenesis of KS and guides preventive and therapeutic specific interventions.

Dr Romy Gadisseur from Clinical Chemist, EuSpLM, Laboratories "Emergency, Allergy, Urolithiasis" at University Hospital of Liège and Vincent Castiglione Ph.D. student at the Clinical Chemistry department of University Hospital of Liège presented their results of distribution of stone composition in Province of Liège (Belgium) according to age and sex [112]. They retrospectively reviewed 1869 urinary stones analyzed between 2010 and 2013 at the laboratory of the CHU of Liège (Belgium). Samples were assessed by infrared spectroscopy, and morphology was used to classify KS in MC types according to Daudon's classification. Among 1869 stones, 69.2% affected men. The peak prevalence was observed between 50 and 60 years of age in both genders. The main constituent was calcium oxalate monohydrate (54.4%), mainly organized as type Ia (94%). Calcium oxalate dihydrate was found in 19.8% samples, with an equal distribution between types IIa and IIb. Uric acid was the 3rd most frequent constituent in men (10.8%), instead of phosphates in women (26.6%). Urinary infection may be the main cause of stone formation in 6% of patients. Multiple morphological types were concomitantly identified in 49.3% of stones. With aging, the proportion of calcium oxalate dihydrate stones decreased, while that of calcium oxalate monohydrate and uric acid increased in both genders.

Prof Fredric Cotton and Agnieszka Pozdzik presented data from retrospective study applying Daudon's MC classification based on stereomicroscopy and infrared spectrophotometry analysis of KS inform the center in Brussels. The analysis was carried out on 5480 samples sent to the laboratory between 2007 and 2013. Among 5027 stones formers, 3549 (71%) were men and 1478 (29%) were women. The main compound observed was calcium oxalate (whewellite 52%, weddellite 23%), followed by calcium phosphate stones (carbapatite 6.8%), uric acid stones (anhydrous uric acid 9.1%), and struvite (2.1%). In 40% of the cases, one single compound accounted for more than 90% of the composition. Two compounds or more were found in 28% and 31% of KS, respectively. The most common associations were weddellite-whewellite-carbapatite (15%), weddellite-whewellite (12.4%) and weddellite-carbapatite (6.1%).

Type Ia was the most common in whewellite stones (91.6%) and type IIa (73%) followed by type IIb (25%) in weddellite stones. Uric acid stones corresponded mainly to type IIIa (52%) and IIIb (46%). Carbapatite defined as type IVa was found in 42% and as type IVb in 32%. Whewellite and weddellite KS predominated in men in all age groups with the highest prevalence between 40 and 50 years. The prevalence of uric acid KS was higher in men peaked between 60 and 70 years. Struvite and carbapatite KS were mostly observed between 40 and 50 in both genders but more frequently in women between 20 and 60 years. To our knowledge, the epidemiology based on M-C analysis reported here has been performed in the largest cohort of KS available in Belgium. Presented data suggests that the leading metabolic disorders involved in lithogenesis in the Brussels population are likely intermittent hyperoxaluria leading to stones of type Ia and hypercalciuria associated with stones of type IIa.

Medical measures for the secondary prevention of nephrolithiasis

Kidney stone disease without treatment is a recurrent illness that represents a major health burden across the globe with associated economic costs. A conservative approach is the key management in all KSF. Pharmacological treatment is indicated in recurrent stone-forming populations [113].

High oral fluid intake must be consumed in all KSF to reduce urinary saturation with respect to stone-forming salts [114]. The consumption of fructose- and phosphoric acid-based soft drinks may increase the risk of KS formation.

A dietary intervention consisting of low sodium ($\leq$100 mEq/day), low animal protein (50 to 60 g/day) with normal calcium intake (1200 mg/day) significantly reduced risk of KS recurrence when compared to low dietary calcium intake (400 mg/day) [113]. However, the role of the low animal protein intake alone on reducing stone recurrence has been shown only in one study. Similarly, the evidence for the role of dietary fiber, low sodium, calcium and purine intake in the recurrence of KS remains circumstantial.

Pharmacological treatment of calcium KSF includes alkali and thiazide diuretics [115, 116]. Alkali treatment is recommended in recurrent calcium oxalate and calcium phosphates as well as UA kidney stone formers, with hypocitraturia or normal urine citrate, distal renal tubular acidosis, chronic diarrhea, drug or diet-induced hypocitraturia. Thiazide diuretics are commonly used in those with hypercalciuric nephrolithiasis. It is preferable to combine potassium alkali treatment with thiazide than potassium chloride supplementation in raising urinary citrate excretion [116].

Allopurinol was shown to be effective in lowering the risk of calcium KS. The effectiveness of the magnesium in reducing the risk of stone has not yet been established.

Challenges in the diagnosis of kidney stones

With careful evaluation and management, the great majority of KS are preventable. Despite vast developments in the radiological, morphoconstitutional and biochemical analyses in the past 5 decades, the incidence, costs, and morbidity of nephrolithiasis are rising, and persistent challenges hinder the optimal diagnosis and KSD management. In particular, recent advances in imaging techniques to identify stone composition and/or extent of Randall's plaque in vivo are promising. Challenges in biochemical analyses of individual urinary parameters, and in computer-based assessment of urinary saturation indices, include a significant overlap in these parameters between stone formers and non-stone formers. Cut-off values for predicting stone recurrence are currently investigated. The morphoconstitutional analysis of KS needs to be more frequently used as it can be very helpful in the evaluation of KS etiology considering the fact the KS contain the fingerprints of metabolic disorders.

Conclusions and outcomes

The symposium on kidney stones and mineral metabolism is currently one of the few dedicated kidney stones meetings to be held internationally on a biannual basis. In 2017, the first meeting brought together clinical and basic researchers, pathologists, nephrologists, urologists and biologists. This model demonstrates how clinical and research collaboration should be facilitated, as it brings together worldwide recognized experts in the diagnosis and treatment of nephrolithiasis. This is of greatest importance for patients and families, specifically those with inherited KSD, as well as to encourage new recruitment of physicians interested in KSD pathophysiology. The symposium provided the available knowledge in KSD but also the future direction in promoting the new advancements in the field.

Acknowledgements We are thankful the Direction department (Profs Jean-Marie De Meyer and Jean-Bernard Gillet, and Mr Fancis de Drée) of Brugmann hospital, Brussels, Belgium for the hosting commodity of the symposium. Our particular acknowledgements go to Mrs Isabelle Poplement and Mrs Leslie Leclercq for her deep involvement in the practical organization of symposium. We greatly appreciate the help Mrs Isabelle Martin, Joelle Watticant and Françoise Devillers from Ergotherapy department at CHU Brugmann.

Funding This symposium was sponsored by scientific grants (MDeon Visa 17/V2/10119/005925) from Nippro Belgique, Amgen Belgique, Baxter Belgique, Vifor Fresenius Medical Care Renal Pharma Belgique, BellcoMedtronic, Menarini Belgique and BioHealth Italy.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest regarding this article's content.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. This article does not contain any studies with animal subjects.

Endorsement European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) endorsed the scientific program of symposium.

References

1. Sakhaee K, Maalouf NM, Sinnott B (2012) Clinical review. Kidney stones 2012: pathogenesis, diagnosis, and management. J Clin Endocrinol Metab 97(6):1847–1860
2. Romero V, Akpinar H, Assimos DG (2010) Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol 12(2–3):e86–e96
3. Shuster J, Scheaffer RL (1984) Economic impact of kidney stones in white male adults. Urology 24(4):327–331
4. Cone EB, Hammill BG, Routh JC, Lipkin ME, Preminger GM, Schmader KE et al (2018) Disproportionate use of inpatient care by older adults with kidney stones. Urology 120:103–108
5. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America P (2012) Prevalence of kidney stones in the United States. Eur Urol 62(1):160–165
6. Zeng G, Mai Z, Xia S, Wang Z, Zhang K, Wang L et al (2017) Prevalence of kidney stones in China: an ultrasonography based cross-sectional study. BJU Int 120(1):109–116
7. Ramello A, Vitale C, Marangella M (2000) Epidemiology of nephrolithiasis. J Nephrol 13(Suppl 3):S45–S50
8. Xu LHR, Adams-Huet B, Poindexter JR, Maalouf NM, Moe OW, Sakhaee K (2017) Temporal changes in kidney stone composition and in risk factors predisposing to stone formation. J Urol 197(6):1465–1471
9. Shavit L, Ferraro PM, Johri N, Robertson W, Walsh SB, Moochhala S et al (2015) Effect of being overweight on urinary metabolic risk factors for kidney stone formation. Nephrol Dial Transpl 30(4):607–613
10. Daudon M (2005) [Epidemiology of nephrolithiasis in France]. Ann Urol (Paris) 39(6):209–231
11. Mandel N, Mandel I, Fryjoff K, Rejniak T, Mandel G (2003) Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. J Urol 169(6):2026–2029
12. Daudon M, Donsimoni R, Hennequin C, Fellahi S, Le Moel G, Paris M et al (1995) Sex- and age-related composition of 10 617 calculi analyzed by infrared spectroscopy. Urol Res 23(5):319–326
13. Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC (2009) Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol 4(4):804–811
14. Maeda S, Naganuma T, Takemoto Y, Shoji T, Okamura M, Nakatani T (2012) Chronic kidney disease in urolithiasis

patients following successful extracorporeal shockwave lithotripsy. Mol Med Rep 5(1):3–6
15. Shang W, Li L, Ren Y, Ge Q, Ku M, Ge S et al (2017) History of kidney stones and risk of chronic kidney disease: a meta-analysis. PeerJ 5:e2907
16. Rule AD, Krambeck AE, Lieske JC (2011) Chronic kidney disease in kidney stone formers. Clin J Am Soc Nephrol 6(8):2069–2075
17. Goldfarb DS, Fischer ME, Keich Y, Goldberg J (2005) A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. Kidney Int 67(3):1053–1061
18. Gambaro G, Vezzoli G, Casari G, Rampoldi L, D'Angelo A, Borghi L (2004) Genetics of hypercalciuria and calcium nephrolithiasis: from the rare monogenic to the common polygenic forms. Am J Kidney Dis 44(6):963–986
19. Edvardsson VO, Palsson R, Indridason OS, Thorvaldsson S, Stefansson K (2009) Familiality of kidney stone disease in Iceland. Scand J Urol Nephrol 43(5):420–424
20. Guerra A, Folesani G, Nouvenne A, Ticinesi A, Allegri F, Pinelli S et al (2016) Family history influences clinical course of idiopathic calcium nephrolithiasis: case-control study of a large cohort of Italian patients. J Nephrol 29(5):645–651
21. Toka HR, Genovese G, Mount DB, Pollak MR, Curhan GC (2013) Frequency of rare allelic variation in candidate genes among individuals with low and high urinary calcium excretion. PLoS One 8(8):e71885
22. Thorleifsson G, Holm H, Edvardsson V, Walters GB, Styrkarsdottir U, Gudbjartsson DF et al (2009) Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. Nat Genet 41(8):926–930
23. Yasui T, Okada A, Urabe Y, Usami M, Mizuno K, Kubota Y et al (2013) A replication study for three nephrolithiasis loci at 5q35.3, 7p14.3 and 13q14.1 in the Japanese population. J Hum Genet 58(9):588–593
24. Oliveira B, Kleta R, Bockenhauer D, Walsh SB (2016) Genetic, pathophysiological, and clinical aspects of nephrocalcinosis. Am J Physiol Renal Physiol 311(6):F1243–F1252
25. Shavit L, Jaeger P, Unwin RJ (2015) What is nephrocalcinosis? Kidney Int 88(1):35–43
26. Michalus I, Rusinska A (2018) Rare, genetically conditioned forms of rickets: Differential diagnosis and advances in diagnostics and treatment. Clin Genet 94(1):103–114
27. Sayer JA, Carr G, Simmons NL (2004) Nephrocalcinosis: molecular insights into calcium precipitation within the kidney. Clin Sci (Lond) 106(6):549–561
28. Taguchi K, Yasui T, Milliner DS, Hoppe B, Chi T (2017) Genetic risk factors for idiopathic urolithiasis: a systematic review of the literature and causal network analysis. Eur Urol Focus 3(1):72–81
29. Halbritter J, Baum M, Hynes AM, Rice SJ, Thwaites DT, Gucev ZS et al (2015) Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. J Am Soc Nephrol 26(3):543–551
30. Braun DA, Lawson JA, Gee HY, Halbritter J, Shril S, Tan W et al (2016) Prevalence of monogenic causes in pediatric patients with nephrolithiasis or nephrocalcinosis. Clin J Am Soc Nephrol 11(4):664–672
31. Daga A, Majmundar AJ, Braun DA, Gee HY, Lawson JA, Shril S et al (2018) Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. Kidney Int 93(1):204–213
32. Pelle A, Cuccurullo A, Mancini C, Sebastiano R, Stallone G, Negrisolo S et al (2017) Updated genetic testing of Italian patients referred with a clinical diagnosis of primary hyperoxaluria. J Nephrol 30(2):219–225
33. Diefenhardt P, Nosko A, Kluger MA, Richter JV, Wegscheid C, Kobayashi Y et al (2018) IL-10 receptor signaling empowers regulatory T cells to control Th17 responses and protect from GN. J Am Soc Nephrol 29(7):1825–1837
34. Cloutier J, Villa L, Traxer O, Daudon M (2015) Kidney stone analysis: "Give me your stone, I will tell you who you are!". World J Urol 33(2):157–169
35. Siener R, Buchholz N, Daudon M, Hess B, Knoll T, Osther PJ et al (2016) Quality assessment of urinary stone analysis: results of a multicenter study of laboratories in Europe. PLoS One 11(6):e0156606
36. Daudon M, Dessombz A, Frochot V, Letavernier E, Haymann JP, Jungers P, Bazin D (2016) Comprehensive morpho-constitutional analysis of urinary stones improves etiological diagnosis and therapeutic strategy of nephrlithiasis. C R Chim 19:1470–1491
37. Reveillaud RJ, Daudon M, Protat MF, Ayrole G (1980) Analysis of urinary calculi in adults. Attempt of correlations between morphology and composition. Eur Urol 6(3):161–165
38. Daudon M, Estepa L, Lacour B, Jungers P (1998) Unusual morphology of calcium oxalate calculi in primary hyperoxaluria. J Nephrol 11(Suppl 1):51–55
39. Sakhaee K, Maalouf NM (2008) Metabolic syndrome and uric acid nephrolithiasis. Semin Nephrol 28(2):174–180
40. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K (2007) Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2(5):883–888
41. Moe OW, Xu LHR (2018) Hyperuricosuric calcium urolithiasis. J Nephrol 31(2):189–196
42. Goldfarb DS, Hirsch J. Hypothesis (2015) Urbanization and exposure to urban heat islands contribute to increasing prevalence of kidney stones. Med Hypotheses 85(6):953–957
43. Ferraro PM, Curhan GC, D'Addessi A, Gambaro G (2017) Risk of recurrence of idiopathic calcium kidney stones: analysis of data from the literature. J Nephrol 30(2):227–233
44. Vervaet BA, Verhulst A, D'Haese PC, De Broe ME (2009) Nephrocalcinosis: new insights into mechanisms and consequences. Nephrol Dial Transpl 24(7):2030–2035
45. Vervaet BA, D'Haese PC, De Broe ME, Verhulst A (2009) Crystalluric and tubular epithelial parameters during the onset of intratubular nephrocalcinosis: illustration of the 'fixed particle' theory in vivo. Nephrol Dial Transpl 24(12):3659–3668
46. Vervaet BA, Verhulst A, De Broe ME, D'Haese PC (2010) The tubular epithelium in the initiation and course of intratubular nephrocalcinosis. Urol Res 38(4):249–256
47. Verhulst A, Asselman M, De Naeyer S, Vervaet BA, Mengel M, Gwinner W et al (2005) Preconditioning of the distal tubular epithelium of the human kidney precedes nephrocalcinosis. Kidney Int 68(4):1643–1647
48. Letavernier E, Vandermeersch S, Traxer O, Tligui M, Baud L, Ronco P et al (2015) Demographics and characterization of 10,282 Randall plaque-related kidney stones: a new epidemic? Medicine (Baltimore) 94(10):e566
49. Verrier C, Bazin D, Huguet L, Stephan O, Gloter A, Verpont MC et al (2016) Topography, composition and structure of incipient randall plaque at the nanoscale level. J Urol 196(5):1566–1574
50. Letavernier E, Daudon M (2018) Vitamin D, Hypercalciuria and kidney stones. Nutrients 10(3):366
51. Letavernier E, Daudon M. Stones (2016) Tolvaptan might prevent kidney stone formation. Nat Rev Urol 13(3):130–131
52. Letavernier E, Kauffenstein G, Huguet L, Navasiolava N, Boudeerlique E, Tang E et al (2018) ABCC6 deficiency promotes development of randall plaque. J Am Soc Nephrol 29:2337–2347
53. Kumakura S, Nakaya I, Sakuma T, Sato H, Soma J (2016) Crystalline cast nephropathy in a patient with IgD lambda myeloma. Clin Exp Nephrol 20(3):491–492

54. Gupta V, El Ters M, Kashani K, Leung N, Nasr SH (2015) Crystalglobulin-induced nephropathy. J Am Soc Nephrol 26(3):525–529
55. Chatchen S, Pongsakul N, Srisomsap C, Chiangjong W, Hongeng S, Svasti J et al (2018) Unravelling pathophysiology of crystalline nephropathy in ceftriaxone-associated acute kidney injury: a cellular proteomic approach. Nephron 139(1):70–82
56. Carbone LG, Bendixen B, Appel GB (1988) Sulfadiazine-associated obstructive nephropathy occurring in a patient with the acquired immunodeficiency syndrome. Am J Kidney Dis 12(1):72–75
57. Sawyer MH, Webb DE, Balow JE, Straus SE (1988) Acyclovir-induced renal failure. Clinical course and histology. Am J Med 84(6):1067–1071
58. Nasr SH, Milliner DS, Wooldridge TD, Sethi S (2014) Triamterene crystalline nephropathy. Am J Kidney Dis 63(1):148–152
59. Santoriello D, Al-Nabulsi M, Reddy A, Salamera J, D'Agati VD, Markowitz GS (2017) Atazanavir-associated crystalline nephropathy. Am J Kidney Dis 70(4):576–580
60. Daudon M, Frochot V, Bazin D, Jungers P (2018) Drug-induced kidney stones and crystalline nephropathy: pathophysiology, prevention and treatment. Drugs 78(2):163–201
61. Cartery C, Faguer S, Karras A, Cointault O, Buscail L, Modesto A et al (2011) Oxalate nephropathy associated with chronic pancreatitis. Clin J Am Soc Nephrol 6(8):1895–1902
62. Chuang YW, Wen MC, Wu MJ, Shu KH, Cheng CH, Yu TM et al (2012) Follow-up and treatment of renal transplantation with nephropathic cystinosis in central Taiwan. Transpl Proc 44(1):80–82
63. Ceballos-Picot I, Perignon JL, Hamet M, Daudon M, Kamoun P (1992) 2,8-Dihydroxyadenine urolithiasis, an underdiagnosed disease. Lancet 339(8800):1050–1051
64. Bollee G, Cochat P, Daudon M (2015) Recurrence of crystalline nephropathy after kidney transplantation in APRT deficiency and primary hyperoxaluria. Can J Kidney Health Dis 2:31
65. Fogazzi GB (1996) Crystalluria: a neglected aspect of urinary sediment analysis. Nephrol Dial Transpl 11(2):379–387
66. Daudon M, Frochot V (2015) Crystalluria. Clin Chem Lab Med 53(Suppl 2):s1479–87
67. Scales CD Jr, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z (2016) Urinary stone disease: advancing knowledge, patient care, and population health. Clin J Am Soc Nephrol 11(7):1305–1312
68. Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR et al (2016) Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol 11(3):488–496
69. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M (2004) ESKD caused by nephrolithiasis: prevalence, mechanisms, and prevention. Am J Kidney Dis 44(5):799–805
70. Alexander RT, Hemmelgarn BR, Wiebe N, Bello A, Morgan C, Samuel S et al (2012) Kidney stones and kidney function loss: a cohort study. BMJ 345:e5287
71. Denburg MR, Jemielita TO, Tasian GE, Haynes K, Mucksavage P, Shults J et al (2016) Assessing the risk of incident hypertension and chronic kidney disease after exposure to shock wave lithotripsy and ureteroscopy. Kidney Int 89(1):185–192
72. El-Zoghby ZM, Lieske JC, Foley RN, Bergstralh EJ, Li X, Melton LJ 3rd et al (2012) Urolithiasis and the risk of ESKD. Clin J Am Soc Nephrol 7(9):1409–1415
73. Gambaro G, Croppi E, Bushinsky D, Jaeger P, Cupisti A, Ticinesi A et al (2017) The risk of chronic kidney disease associated with urolithiasis and its urological treatments: a review. J Urol 198(2):268–273
74. Spatola L, Angelini C, Badalamenti S, Maringhini S, Gambaro G (2017) Kidney stones diseases and glycaemic statuses: focus on the latest clinical evidences. Urolithiasis 45(5):457–460
75. Worcester EM, Parks JH, Evan AP, Coe FL (2006) Renal function in patients with nephrolithiasis. J Urol 176(2):600–603 **(discussion 3)**
76. Connors BA, Evan AP, Willis LR, Blomgren PM, Lingeman JE, Fineberg NS (2000) The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. J Am Soc Nephrol 11(2):310–318
77. Petrucci I, Clementi A, Sessa C, Torrisi I, Meola M (2018) Ultrasound and color Doppler applications in chronic kidney disease. J Nephrol 31(6):863–879
78. Zerwekh JE, Hwang TI, Poindexter J, Hill K, Wendell G, Pak CY (1988) Modulation by calcium of the inhibitor activity of naturally occurring urinary inhibitors. Kidney Int 33(5):1005–1008
79. Ettinger B, Citron JT, Livermore B, Dolman LI (1988) Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol 139(4):679–684
80. Norman DA, Zerwekh JE, Pak CY (1981) An apparent 1,25-dihydroxyvitamin D-independent stimulation of intestinal calcium absorption in patients with Paget disease of bone during a short-term diphosphonate therapy. Metabolism 30(3):290–292
81. Tebben PJ, Milliner DS, Horst RL, Harris PC, Singh RJ, Wu Y et al (2012) Hypercalcemia, hypercalciuria, and elevated calcitriol concentrations with autosomal dominant transmission due to CYP24A1 mutations: effects of ketoconazole therapy. J Clin Endocrinol Metab 97(3):E423–E427
82. Kaufman DW, Kelly JP, Curhan GC, Anderson TE, Dretler SP, Preminger GM et al (2008) Oxalobacter formigenes may reduce the risk of calcium oxalate kidney stones. J Am Soc Nephrol 19(6):1197–1203
83. Ricagno S, Jonsson S, Richards N, Lindqvist Y (2003) Formyl-CoA transferase encloses the CoA binding site at the interface of an interlocked dimer. EMBO J 22(13):3210–3219
84. Siener R, Bangen U, Sidhu H, Honow R, von Unruh G, Hesse A (2013) The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int 83(6):1144–1149
85. Maalouf NM, Moe OW, Adams-Huet B, Sakhaee K (2011) Hypercalciuria associated with high dietary protein intake is not due to acid load. J Clin Endocrinol Metab 96(12):3733–3740
86. Ticinesi A, Guerra A, Allegri F, Nouvenne A, Cervellin G, Maggio M et al (2018) Determinants of calcium and oxalate excretion in subjects with calcium nephrolithiasis: the role of metabolic syndrome traits. J Nephrol 31(3):395–403
87. Adami S, Marcocci C, Gatti D (2002) Epidemiology of primary hyperparathyroidism in Europe. J Bone Miner Res 17(Suppl 2):N18–N23
88. Bilezikian JP, Silverberg SJ (2004) Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med 350(17):1746–1751
89. Lal G, Clark OH (2003) Primary hyperparathyroidism: controversies in surgical management. Trends Endocrinol Metab 14(9):417–422
90. Bilezikian JP, Potts JT Jr, Fuleihan Gel H, Kleerekoper M, Neer R, Peacock M et al (2002) Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 87(12):5353–5361
91. Bilezikian JP, Potts JT Jr (2002) Asymptomatic primary hyperparathyroidism: new issues and new questions—bridging the past with the future. J Bone Miner Res 17(Suppl 2):N57–N67
92. Ruda JM, Hollenbeak CS, Stack BC Jr (2005) Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 132(3):359–372

93. Daudon M, Lacour B, Jungers P (2006) Influence of body size on urinary stone composition in men and women. Urol Res 34(3):193–199
94. Sakhaee K (2008) Nephrolithiasis as a systemic disorder. Curr Opin Nephrol Hypertens 17(3):304–309
95. Sakhaee K (2014) Epidemiology and clinical pathophysiology of uric acid kidney stones. J Nephrol 27(3):241–245
96. Maalouf NM, Cameron MA, Moe OW, Sakhaee K (2010) Metabolic basis for low urine pH in type 2 diabetes. Clin J Am Soc Nephrol 5(7):1277–1281
97. Daudon M, Traxer O, Conort P, Lacour B, Jungers P (2006) Type 2 diabetes increases the risk for uric acid stones. J Am Soc Nephrol 17(7):2026–2033
98. Fernandez A, Fuller A, Al-Bareeq R, Nott L, Razvi H (2013) A comparison of the metabolic profiles of diabetic and non-diabetic uric acid stone formers. Can Urol Assoc J 7(3–4):E190–E192
99. Nikiforova VJ, Giesbertz P, Wiemer J, Bethan B, Looser R, Liebenberg V et al (2014) Glyoxylate, a new marker metabolite of type 2 diabetes. J Diabetes Res 2014:685204
100. Burdin DV, Kolobov AA, Brocker C, Soshnev AA, Samusik N, Demyanov AV et al (2016) Diabetes-linked transcription factor HNF4alpha regulates metabolism of endogenous methylarginines and beta-aminoisobutyric acid by controlling expression of alanine-glyoxylate aminotransferase 2. Sci Rep 6:35503
101. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ (1997) Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 126(7):497–504
102. Sakhaee K, Poindexter JR, Griffith CS, Pak CY (2004) Stone forming risk of calcium citrate supplementation in healthy postmenopausal women. J Urol 172(3):958–961
103. Karp HJ, Ketola ME, Lamberg-Allardt CJ (2009) Acute effects of calcium carbonate, calcium citrate and potassium citrate on markers of calcium and bone metabolism in young women. Br J Nutr 102(9):1341–1347
104. Green JH, Booth C, Bunning R (2003) Acute effect of high-calcium milk with or without additional magnesium, or calcium phosphate on parathyroid hormone and biochemical markers of bone resorption. Eur J Clin Nutr 57(1):61–68
105. Ketha H, Singh RJ, Grebe SK, Bergstralh EJ, Rule AD, Lieske JC et al (2015) Altered calcium and vitamin D homeostasis in first-time calcium kidney stone-formers. PLoS One 10(9):e0137350
106. Hu H, Zhang J, Lu Y, Zhang Z, Qin B, Gao H et al. Association between circulating vitamin D Level and urolithiasis: a systematic review and meta-analysis. Nutrients. 2017;9(3):301
107. Bambach CP, Robertson WG, Peacock M, Hill GL (1981) Effect of intestinal surgery on the risk of urinary stone formation. Gut 22(4):257–263
108. Kumar R, Lieske JC, Collazo-Clavell ML, Sarr MG, Olson ER, Vrtiska TJ et al (2011) Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery. Surgery 149(5):654–661
109. Lieske JC, Mehta RA, Milliner DS, Rule AD, Bergstralh EJ, Sarr MG (2015) Kidney stones are common after bariatric surgery. Kidney Int 87(4):839–845
110. Canales BK, Hatch M (2014) Kidney stone incidence and metabolic urinary changes after modern bariatric surgery: review of clinical studies, experimental models, and prevention strategies. Surg Obes Relat Dis 10(4):734–742
111. Pareek G, Armenakas NA, Panagopoulos G, Bruno JJ, Fracchia JA (2005) Extracorporeal shock wave lithotripsy success based on body mass index and Hounsfield units. Urology 65(1):33–36
112. Castiglione V, Jouret F, Bruyere O, Dubois B, Thomas A, Waltregny D et al (2015) [Epidemiology of urolithiasis in Belgium on the basis of a morpho-constitutional classification]. Nephrol Ther 11(1):42–49
113. Sakhaee K (2017) Medical measures for secondary prevention of urolithiasis. Eur Urol Focus 3(1):10–12
114. Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CY (1993) The potential role of salt abuse on the risk for kidney stone formation. J Urol 150(2 Pt 1):310–312
115. Sakhaee K, Williams RH, Oh MS, Padalino P, Adams-Huet B, Whitson P et al (1993) Alkali absorption and citrate excretion in calcium nephrolithiasis. J Bone Miner Res 8(7):789–794
116. Gambaro G, Croppi E, Coe F, Lingeman J, Moe O, Worcester E et al (2016) Metabolic diagnosis and medical prevention of calcium nephrolithiasis and its systemic manifestations: a consensus statement. J Nephrol 29(6):715–734