1. Introduction

Urolithiasis (UL) is one of the most common diseases, with worldwide increasing incidence and prevalence. The pathogenesis of calcium oxalate (CaOx) UL, which accounts for >80% of all urinary stones, is only incompletely understood. This paper reviews trends in epidemiology and current concepts regarding the pathogenesis and pathophysiology of urinary stone disease.

2. Evidence acquisition

Urinary stone formation is a common disease with an increasing incidence and prevalence worldwide that appears even more pronounced in industrialized countries [2,4–10]. Such observations seem to underscore the impact of lifestyle and dietary choices as well as access to better medical care for urinary stone formation.

Renal stone formation and the predominant chemical stone composition are age and gender dependent [11]. Most stones are formed in older patients. However, clinical observations have indicated not only a changing frequency and composition of urinary calculi but also a shift in gender- and age-related incidences [11–13]. Urinary stone disease remains rare in children with a stable overall incidence in most series [14]. As in adults, factors implicated in the metabolic syndrome complex such as obesity pose risks for urinary stone formation in children [15].

Although some authors have suggested the impact of climate change [16,17], changing lifestyle and dietary choices are the more probable cause of the increasing incidence and prevalence of UL. Taylor and Curhan demonstrated a correlation of body weight and urinary calcium excretion [18]. In two large epidemiologic series, they also reported
diabetes as an independent risk factor for the development of kidney stones [4,19,20]. Siener confirmed such findings in studies on recurrent stone formers [21]. Changing chemical stone compositions have been reported, possibly as results of the described changes of lifestyle [22,23].

Calcium-containing calculi are predominant in males and females [11,24,25]. However, UL remains a disease with a clear predominance in males for all stone compositions except for infection stones. In our own series, including >200 000 stone analyses, this difference increased over the observation period with a 2.7:1 male-to-female ratio for the most common calcium-containing calculi [26]. Daudon et al. showed a male predominance for CaOx and uric acid, and a female predominance for calcium phosphate (CaPh) and struvite stones [11]. Approximately 15% of all stone formers produce CaPh stones [27]. Up to a quarter of those CaPh stones contain calcium monohydrogen phosphate (brushite), which is difficult both to treat and to prevent [28]. Our own series demonstrated an increased prevalence of brushite [26] (Fig. 1).

Currently, uric acid composition seems to be the second most common stone in both genders. Daudon et al reported a significant increase in uric acid stone frequency, whereas in our own series the rate remained stable [11,26].

Stones due to infection have clearly declined over the years, attributable to improved medical care. Trinchieri et al. reported a 15-yr series from Italy of stone analyses with a low number of infection stones [29]. Marickar and Vijay reported a decrease of infection stones in females despite an overall increase of urinary stone formation [7]. The decreasing number of staghorn stones in Europe supports this observation because urinary tract infections are the most common cause of such large renal calculi [30].

Cystine stones, formed by patients with cystinuria, account for only a small percentage of all urinary stones [26]. The higher peak in younger ages is in accordance with the first stone event, which typically occurs in the 2nd decade of life, whereas the lower frequency at older ages may be a result of preventive measures [31].

Interestingly, our German series demonstrated significant regional differences [26]. Although calculi containing uric acid were more prevalent in southern Germany, we observed a significantly higher frequency of stones due to infection in eastern Germany. We can only hypothesize an explanation for these findings. A diet based more heavily on red meat may explain the higher rate of uric acid calculi in southern Germany. The higher frequency of infection stones in the eastern part of the country (formerly the socialist German Democratic Republic) is surprising and cannot be adequately explained. However, this finding suggests that differences in medical care do exist.

3. Evidence synthesis

3.1. Pathogenesis and pathophysiology

Urinary stone formation is a result of different mechanisms. Whereas exceeding supersaturation (ie, free stone formation) is the cause of uric acid or cystine calculi, infection stones result from bacterial metabolism [32]. The formation of the most common fraction, the calcium-containing calculi, is more complex and, surprisingly, is not yet completely understood. Recent evidence suggests that both free and fixed stone formation is possible [33]. The long accepted simple explanation of exceeding the solubility product of lithogenic substances in the urine cannot describe these

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**Fig. 1 – Frequency of hydroxyapatite, brushite, and calcium oxalate components in urinary stones, 1980–2004 (n = 111 196).**
complex processes sufficiently [33]. Deviating from the hypothesis that claims the initial crystal deposition takes place in the lumens of renal tubules [34–36], new insights suggest a primary plaque formation in the interstitial space of the renal papilla [37,38]. CaPh crystals and organic matrix initially are deposited along the basement membranes of the thin loops of Henle and extend further into the interstitial space to the urothelium, constituting the so-called Randall plaques, which are regularly found during endoscopy of patients who form CaOx stones (Fig. 2). These CaPh crystals seem to be the origin for the development of future CaOx stones, which form by the attachment of further matrix molecules and CaOx from the urine to the plaque [39]. The driving forces, the exact pathogenetic mechanisms, and the involved matrix molecules are still largely unknown. Completely different pathomechanisms obviously lead to the common clinical diagnosis of “CaOx stone former.”

Stoller et al raised another interesting hypothesis. They suggested an even closer participation of the vasa recta in the lithogenesis of kidney stones [40]. The descending and ascending vasa recta are vulnerable because of the hypoxic and hyperosmolar environment in the papillary tip and because the blood flow in the papillary tip changes from a laminar to a turbulent flow as the ascending vasa recta repeatedly bifurcates [41]. They proposed this could lead to atherosclerotic-like lesions and calcifications in the wall of the vasa recta. These calcifications could then erode to papillary interstitium and grow there, supported by cellular promotors [42]. The close participation of the vasa recta has led to a new hypothesis regarding the role of vascular phenomena in the lithogenesis of kidney stones.

3.2. Key role of Randall plaques

Randall plaques are thought to be involved in idiopathic CaOx stone formation. Seventy years ago, Randall described calcifications within the renal papilla that he found in 20% of autopsies [43]. These calcifications were made of CaPh (apatite). Randall proposed that the plaques are precursors of urinary stones. His idea was lost for decades until Evan et al were able to show that such plaques are present in all idiopathic CaOx stone formers but not in healthy controls [38,44,45]. When attached stones were removed from the renal papilla, they had the impression that the plaques were the connection of the stones to the papilla. Microscopic computed tomography examinations of CaOx stones confirmed this hypothesis by demonstrating the presence of apatite at the former attachment side [46]. Matlaga et al demonstrated a positive correlation of the frequency of stone recurrences and the total papillary surface covered by plaques [45]. Scanning microscopy of these plaques confirmed that the initial site of crystal deposit is within the base membrane of the thin loop of Henle, as hypothesized by Evan et al [38,47]. Intratubular crystallization was not found within the renal tubules or collecting ducts in idiopathic CaOx stone formers.

Although the site of stone formation has become clear, the initial trigger for crystallization remains under discussion. A multifactorial process seems to be the most probable. An increased urinary calcium excretion appears to play an important role because the measured papillary coverage correlates with urinary calcium and urine pH [48]. Earlier examinations showed higher calcium and oxalate concentrations within the renal papilla than within the renal cortex, medulla, or urine [49]. An acidic urinary pH leads to an increased bicarbonate resorption into the renal medulla and a consecutive increasing interstitial pH that may promote apatite depletion [45].

Recent findings have helped us understand the mechanism of CaOx stone formation on the Randall plaques (which are separated from the urine by the urothelial layer) [47,50]. Stones derived from biopsies of renal papillae were evaluated by immunohistochemistry, scanning microscopy, and infrared spectroscopy. These examinations demonstrated that the urothelium was lost at the attachment side. Organic matrix (mainly Tamm-Horsfall protein and osteopontin) and crystals formed belts that are obviously required to allow further crystal depletion and consequently CaOx stone formation.

4. Conclusions

UL is a common disease with an increasing incidence and prevalence worldwide. Lifestyle and dietary choices implicated in the complex of the metabolic syndrome are important factors contributing to such developments. The pathogenesis and pathophysiology of CaOx stones, the most common urinary stones, is still incompletely understood. Recent evidence suggests a primary interstitial apatite crystal formation (Randall plaque) that secondarily leads to CaOx stone formation.

Conflicts of interest

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**References**


