Encrustation in Urinary Stents

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1   Introduction

Insertion of a ureteral stent is an acute measure to restore the urinary flow from the kidney to the bladder in cases of acute or chronic obstruction or a functional disturbance of ureteral peristalsis. In cases with chronic obstruction and poor prognosis due to surgical or anesthetic inoperability or sometimes patient preference, ureteral stenting may be used as a permanent treatment. In such cases, regular exchange of the ureteral stent at specified intervals is necessary and constitutes a minimally invasive endourological procedure.

With long-standing ureteral stenting, the problems of stent encrustation, biofilm formation, and bacterial colonization become important. Excessive stent encrustation to stent blockage and, consequently, pain, fever, renal infection, impairment of renal function and even renal failure.

Encrustations of urinary stents are due to the crystallization of soluble minerals in urine, predominantly calcium oxalate salts [1]. The quantification of this process is highly individualized. Patients with a high excretion of crystal-forming ions in the urine tend to have fast and excessive formation of encrustations on any stent.

This process can occur without significant bacterial contamination but facilitates the adherence, persistence and multiplication of bacteria in biofilms.

Uropathogenic microorganisms (usually enterobacteria) are either introduced into the bladder when a catheter is inserted, or they migrate into the bladder along a transurethral catheter over time. From the bladder, bacteria ascend through the ureter and especially along a ureteral stent into the kidneys. This

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Table 1 Natural defense mechanisms of the urinary tract

Commensal flora
Urinary flow (ureteral peristalsis)
Skin and mucous membrane
Bladder mucosa: Mucin production
Tamm-Horsefall glycoprotein
Local immune responses

Implants are exempted from those and therefore prone to encrustations

catheter-associated urinary tract infection (CAUTI) is associated with the long-term use of indwelling transurethral bladder catheters [2]. With an indwelling bladder catheter, bacterial colonization will occur within a few days. This problem is clinically highly relevant since ureteral stenting and the use of indwelling bladder catheters are often necessary and combined after urological surgical procedures. This inevitably leads to a high rate of contamination and, consequently, bacteriuria. Bacteria will usually spread throughout the urinary tract but with an unimpeded urinary flow and normal ureteral and bladder function this usually does not lead to clinical problems.

However, with the formation of biofilms on urological implants there will be bacterial colonization. Bacteria are protected from the natural local defense mechanisms of the urinary tract in those biofilms (Table 1). Not only will this lead to more clinically relevant urinary tract infections, but antibiotics are also less effective because they cannot adequately reach bacteria in biofilms. Furthermore, bacteria incorporated in biofilms have a reduced metabolic rate which further reduces the efficacy of most antibiotics. As a result, bacteria in biofilm develop antibiotic resistance more quickly [3, 4].

1.1 Bacteria and Biofilm Formation

Biofilms develop when microorganisms settle in the area between two different phases and are immobilized in a matrix of extracellular polymeric substances (EPS) [5]. These cannot be effectively cleared neither by humoral and cellular immune defense mechanisms nor by antibiotics. Biofilm development can be separated into four such phases (Fig. 1):

1. Reversible aggregation of proteins, polysaccharides and macrolide molecules.
    The binding of proteins to the catheter surface depends on the catheter material (surface energy, mechanical properties and morphology), electrostatic interactions and the composition of the surrounding medium [4]. Within minutes, a dense formation, the *conditioning film*, develops on the substrate [6, 7].
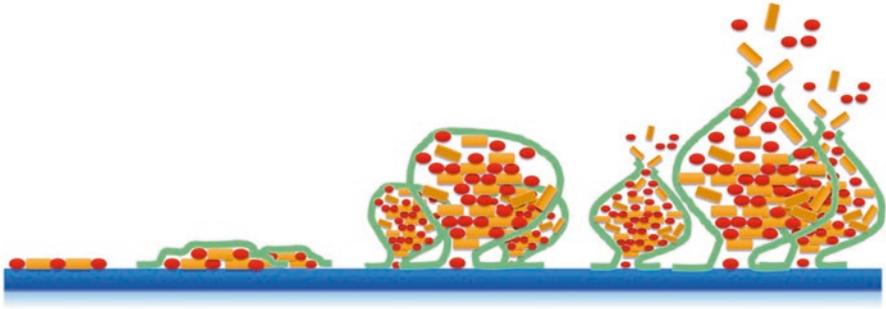
Fig. 1 Biofilm development in four phases

2. Irreversible apposition of proteins and bacteria.

     Bacteria reach the substrate through electrostatic interactions [8, 9]. The production of extracellular polymeric substances (EPS) is influenced in the now closed system by *quorum sensing*, a regulatory system which requires a certain cell density of the same species of bacteria [10].
3. Development of a mature biofilm.

     With further growth, the three-dimensional macro-colonies accumulate to form a bacterial layer. Bacterial immobilization is highest in the close vicinity of the material surface [11].
4. Biofilm spread through degradation of matrix polymers.

     With increasing maturation of the biofilm, cells or clusters of cells can separate and slough from the biofilm. Through the release of enzymes, bacteria can actively leave the biofilm and migrate [12, 13].

1.2 Physicochemical Aspects of Urinary Stents Encrustation and Stone Formation

Multiple influences on the composition of the bacterial mix in a biofilm lead to a heterogeneous biofilm development. Although bacteria are predominant, pathological crystallization may develop and lead to encrustations on catheter materials even without significant microbial presence.

     Regarding the crystallization process (formation of urinary stones) there are different theories:

- Oversaturation of the urine with crystal forming ions (nucleation),
- formation of stone matrix with secondary crystallization of complex macromolecules on the surface,
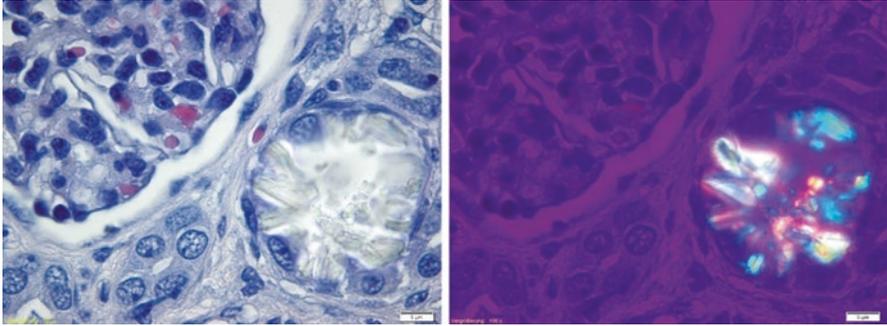
Fig. 2 Histology showing renal kidney injury in a porcine model. Induction of calcium oxalate crystallization (hydroxy-L-proline). No encrustations were seen on the indwelling ureteral stent over 6 weeks. Left: hematoxylin-eosine, 40×; right: polarized light, 40×. BX43 lens UPLSAPO 2 40×/0,95, BX-POL and U-GAN, Olympus

- formation of Randall plaques,
- relative lack of inhibitors or oversupply of promoters of crystallization,
- idiopathic crystallization of calcium oxalate.

Crystallization is influenced by many exogenous and endogenous factors in a multifactorial way. It is thus the result of a complex interaction of many physicochemical and biochemical processes. For the development of urinary stones, the initiating mechanism could be the formation of poly-crystalline in the distal tubules of nephrons. However, crystaluria does not necessarily imply the development of urinary stones. Microscopic crystals are commonly excreted in the urine by healthy individuals with urinary oversaturation (Fig. 2).

The essential factor is the balance between lithogenic and inhibitory substances in the urine. If this equilibrium is disturbed, urinary oversaturation with lithogenic substances will result in spontaneous homogeneous nucleation. Crystals with the same structure will bind to initial aggregates and finally stones. If catheter material or crystals are present in urine, macromolecular urinary compounds will lead to heterogeneous nucleation depending on the degree of oversaturation (metastable oversaturation).

Calcium oxalate, calcium phosphate, magnesium phosphate and uric acid are the minerals that most commonly crystallize in urine [14] (Table 2).

Urinary compounds can modulate the process of crystal nucleation, aggregation and encrustation on urinary stents. These comprise compounds normally present in urine such as the Tamm-Horsefall proteins, glycosaminoglycanes and pyrophosphates [17]. Some of these may have inhibitory as well as promotive effects on nucleation and aggregation. This is discussed with some controversy in the literature [18–21]. Low molecular weight substances such as zinc, magnesium, sulfate

Table 2 Composition of urinary stones [15, 16]

Stone type	Chemical composition	Mineral	Population (%)
Calcium oxalate	Calcium oxalate-monohydrate	Whewellite	70–80
	Calcium oxalate-dihydrate	Weddellite	42
Calcium phosphate	Calcium phosphate	Apatite	30
	Calcium hydrogen phosphate-dihydrate	Brushite	1
	Tricalcium phosphate	Whitlockite	<0.1
	Carbonate apatite	Dahllite	1
Magnesium-ammonium-phosphate	Magnesium-ammonium-phosphate-hexahydrate	Struvite	6
	Magnesium hydrogen-phosphate-trihydrate	Newberyite	<0.1
Uric acid and urate	Uric acid	Uricite	10
	Uric acid-monohydrate	Uricite (mono)	0.1
	Uric acid-dihydrate	Uricite (ortho)	6
	Ammonium hydrogenurate		0.5
Genetically determined	Cystine	Uricite (hexa)	0.4
	Xanthine		<0.1
	2,8-dihydroxyadenine		<0.1

and pyrophosphate bind to calcium and form soluble complexes and do therefore have an inhibitory influence on crystallization.

2 Risks Factors and Complications

2.1 Risks Factors and Complications of Urinary Stone Formation

A polygenetic defect in combination with other facilitating factors (e.g. dietary and climatic conditions) can lead to urolithiasis [22]. Important cofactors are hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria as well as a lack of inhibitory substances [23]. Idiopathic hypercalciuria is the most common etiological factor for calcium stones. In addition, some physiological conditions such as pregnancy influence the urine composition [24]. Pathological conditions such as renal diseases, especially glomerular changes, or disturbances of urine transportation can lead to urinary stone formation. The latter can result from upper or lower urinary tract obstruction, renal dystopia (nephroptosis, pelvic kidney), other malformations such as horse-shoe kidney, ureteroceles, vesico-ureteral reflux, neurogenic bladder dysfunction, or immobilization (e.g. after a fracture).

2.2 Risk Factors and Complications of Encrustations on Stents and Catheters

Pathophysiology of urolithiasis and catheter encrustation are closely related. Studies have shown that the indwelling time of a catheter is the most important risk factor for oxalate-dependent encrustations. However, there is no significant correlation between the volume of encrustation and catheter-associated symptoms [25]. Yet, studies looked at the quantification of encrustations depending on the indwelling time, the differentiation of bacterial colonization, and risk factors associated with these processes [26–29]. Roupret et al. found for ureteral stents with a mean indwelling time of 55.5 days a correlation between stone composition and catheter encrustation of over 70% [30].

Catheter encrustations occur faster in the presence of infection than oxalate-dependent encrustations, and are also associated with risk factors. An important risk factors is residual bladder urine (incomplete bladder emptying) in the presence of an implant, leading to infections. Other risk factors are inflammatory urinary tract obstruction, neurogenic bladder dysfunctions, and urinary diversions using intestinal loops, such as an ileal conduit [31]. This may be further aggravated by additional renal conditions such as distal tubular acidosis, hyperphosphaturia, or medullary sponge kidneys [32].

One important mechanism of biofilm formation is the infection with urease-producing bacteria. Broomfield et al. [33] investigated the capacity of urease-positive bacteria to induce encrustations on ureteral implants. They found that Proteus mirabilis, Proteus vulgaris und Providencia rettgeri have the highest urease activity and induce the highest rate of encrustations. Urease leads to production of ammonia through hydrolysis of urea, with an increase in urinary pH. The alkaline milieu leads to increased crystallization of magnesium-ammonium-phosphate (struvite) as well as calcium-hydroxyapatite (apatite) [34]. Due to improved urological diagnostics, the relative proportion of infectious stones (struvite) has been lowered to 6% of all urinary stones (Table 2). In urological guidelines, there is consensus that in view of the danger of life-threatening infections and/or renal damage as well as the high rate of recurrence, infectious stones and the associated implants should be completely removed [35–38].

In studies of biofilm quantification, Ganderton et al. found that there is no clear relationship between indwelling time and biofilm mass [39]. Presumably there is a relationship with the colonizing ability of the primary bacterial species that settles on the biofilm. Also, catheter design may have important implications for urinary flow through and around the catheter, affecting encrustation formation [40].

An important point would be the contamination-free ureteral stent extraction [41]. Transurethral extraction lead to bacterial contamination from the distal urethra. In addition, catheter encrustations might be dislodged. This is in line with studies that have shown that the rate of bacterial colonization with ureteral stents as well as urethral catheters is higher than the rate of urinary infections [42, 43]. Thus, routine urine cultures are not predictive of catheter cultures.

3 Preventive Strategy of Encrustations and Biofilm Formation

The surface characteristics of a biomaterial (e.g. smoothness of surface, electric charge) as well as the virulence factors of microorganisms, and the presence of adhesins all determine the time course and characteristics of biofilm formation. Most urinary stents are made of polymer mixtures with characteristics that are intended to reduce encrustations [44]. These mixtures are often proprietary, but are usually based on polyurethane (Silhouette®, Bardex® and Tecoflex®). There are also other polymer combinations that can be used such as hydrogel with urethane, silicone, polyvinyl chloride (Aquavene®), styrole, ethylene-butylene, styrole-block copolymers (C-Flex®) and polyester (Silitek®) [45]. Currently used biocompatible polymers, e.g. Elastollan, Styroflex and Greenflex have good mechanical stability and flexibility, with antiadhesive properties and can be used for thin-walled catheters with good urine drainage [46].

Additional compounds need to be added to these basic materials to provide for x-ray opacity. This usually reduces the mechanical flexibility. Usually, 25–30% barium sulfate, a biocompatible salt with high electron density is used for this purpose.

Another way to reduce the degree of encrustation and bacterial adhesions is to coat the catheter surface with different materials. For urinary stents, surface coatings with covalently bound heparin, polytetrafluoroethylene (PTFE), hydrogels, plasma-bound carbon (DLC—diamond-like carbon), or urease-inhibitors can be used [47]. Strategies to reduce microbial adhesions, to induce bactericidal properties (contact killing), to impede the 'quorum sensing' of microbes, and generally to interfere with the initial adhesion process include the formation of a surface film or the release of a bactericidal compound including antibiotics, bacteriophages, metal oxide nanoparticles, other meta ions, and carbon compounds, ionic polymers, as well as polymers and biofilms with non-pathogenic bacteria. Studies with silver nanoparticles and with hydrophilic poly(p-xylylene) (PPX-N) coated catheters found a reduced rate of biofilm formation and reduced bacterial adhesions [48, 49]. Watterson et al. Reported that the coating of urinary stents with enzymes metabolizing oxalate significantly reduced encrustations [50].

Whilst urinary stents impregnated with and releasing e.g. silver ions, hydrogel or antibiotics significantly delayed bacterial adherence in the first days, they did not reduce the rate of significant infections and had no clinical benefit in long-term indwelling catheters. Furthermore, the long-term antibiotic release from stent material might lead to bacterial resistance which can have serious clinical consequences.

Concerning long-term indwelling catheters, surface coatings with covalent bindings seem to hold some promise. Surfaces with double-ion polymers such as phosphorylcholine [51] and covalently bound heparin have been tested [52]. Another class of materials are antibacterial cationic polymers. The contact-active covalently bound coating absorbs proteins and bacteria with a negatively charged cell membrane or cell wall and develops antimicrobial activity through high hydrophilicity with high ionic charges [53].

4   Current Methods for Reducing Encrustation
and Biofilm Formation

As an alternative to conventional implants, biodegradable ureteral stents (BUS) may avoid the procedure of transurethral catheter removal. Another theoretical advantage is the constantly changing material surface which impairs the development of a conditioning biofilm and thus reduces the interaction of the material with microbes. Biodegradable implants consist of several natural and synthetic polymers, whereby the most important biological degrading process is hydrolysis. Barros et al. developed the HydrUStent®. This ureteral stent is completely dissolved after 10 days in urine. X-ray opacity is however given during the first 24 h only [54]. The BraidStent®, a heparin-coated polyurethane ureteral stent has an in-dwelling time of up to 6 weeks in animal tests. The heparin coating allows for an early reduction in bacterial colonization. However, this effect is limited in the long term [55].

Champagne et al. examined the degradation of zinc compounds in artificial urine to try to circumvent the limitations of alloys based on iron and magnesium regarding biocompatibility and controlled degradation under physiological conditions. Zinc alloys are degraded more slowly than magnesium alloys and might be an ideal biomaterial to reduce bacterial adhesions and encrustations on stents [56].

Currently, systems on the basis of computer-based fluid analysis and microfluid models (stent-on-chip, microfluidic chips) are being developed to examine and simulate the flow of urine in a stented ureter. These models are also intended to examine the flow in the presence of additional obstruction, i.e. through encrustation. With changes in the thickness of the stent wall and the design of the side holes significant reductions in particle formation could be achieved [57–59]. Future simulation systems will take a variety of pathological reactions of the stented and the obstructed ureter into account [60].

5   Current Methods for the Examination of Encrustation
and Biofilm on Urinary Stents

Elwood et al. observed that conditioning biofilms on urinary stents contain calcium-binding proteins, among them uromodulin, and that these can serve as a nidus for further crystalline growth and encrustation. These proteins were the same on different stent materials and in different patients. This seems to indicate that the physical properties of the stent surface and not the interaction between bacterial adhesins and urinary proteins are the main determinants for bacterial interactions with stent material [61].

Rebl et al. examined the relationship between physical properties of polymer surfaces and their ability to withstand encrustations. The important parameters to characterize the surfaces were:

- contact angle,
- zeta potential,
- morphology.

The contact angle between a fluid drop and a plane surface is a measure for hydro-philicity. Synthetic urine with a pH of 6.5 was used. The zeta potential describes a specific surface charge which develops between in a watery solute on the interface between a solid material and the watery solution. The comparative analyses in the screening model did show that the negative surface charge of about −60 mV and the hydrophilicity of the polymer (<85°) correlated with a reduced amount of encrusta-tions. The main components of infection stones are struvite with a surface charge of −17.5 mV and carbonate apatite with −16 mV surface charge at a pH of 8.0 [62].

Morphological examinations of stent encrustations are preferably carried out by means of scanning electron microscopy (SEM), energy dispersive X-ray spectros-copy (EDX), and Fourier-transform infrared spectroscopy (FTIR) and show the
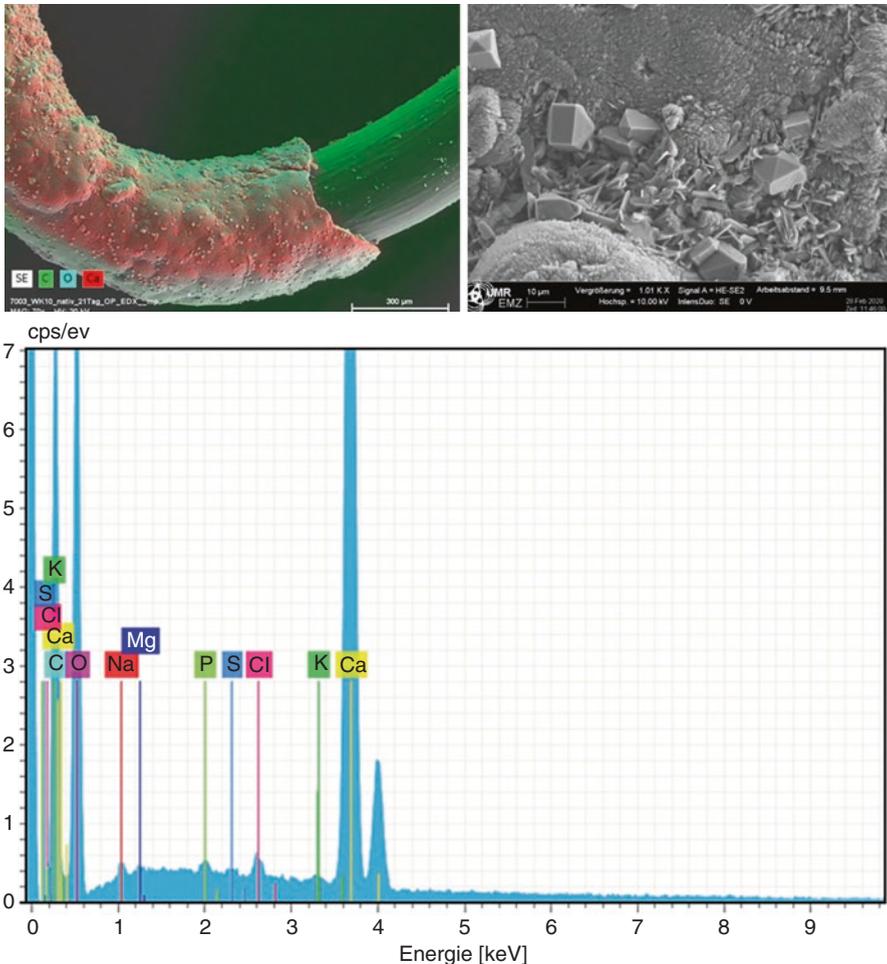

Fig. 3 EDX analysis of encrustations on a ureteral stent (rat). Top left, the mapping shows the elements Ca, C, and O, which are calcium-containing crystals. Top right, SEM image shows a rough surface with calcium oxalate crystals. Bacterias find good conditions here. Bottom: the line spectrum shows the Ca- and P-containing matrix of calcium oxalate and a small proportion of calcium phosphate. FE-SEM Merlin VP compact (Zeiss) with EDX detector XFlash 6/30 (Bruker)
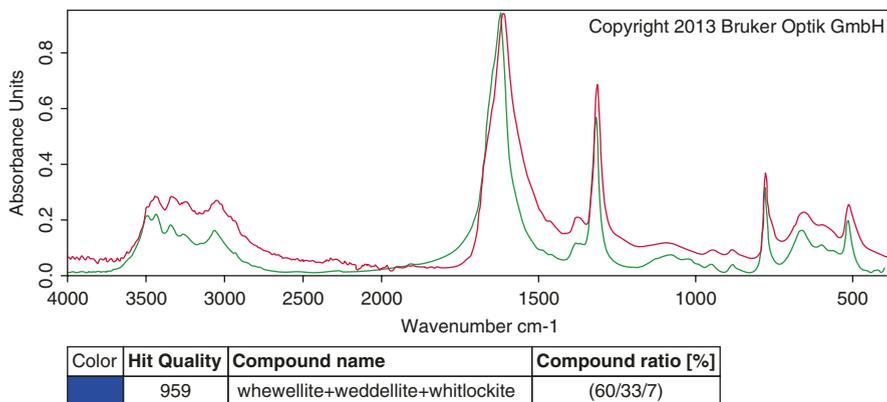
Color	Hit Quality	Compound name	Compound ratio [%]
	959	whewellite+weddellite+whitlockite	(60/33/7)

Fig. 4 FTIR analysis of encrustations on a ureteral stent (Fig. 3) in a rat model. Measured absorption spectra of the mineral deposits in red. Absorption spectra of the OPUS reference library are shown in blue. The encrustation consists of calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddellite) and tricalcium phosphate (whitlockite) 60/33/7. ALPHA FTIR spectrometer, OPUS™ library, Bruker

characteristic interactions of the catheter surface with the surrounding urine in clinical studies. Figures 3 and 4 show the morphological examination of stent encrustations in the rat. The analyses of the surface morphology of the materials showed a mixture of calcium oxalate with the typical dumbbell or envelope appearance, some granular carbonate apatite crystals of some micrometers in size. Fluid properties within the lumen and on the surface of the catheter are different and variable. The rough surface of the polymer can facilitate bacterial growth. Adherent bacteria covered by crystals are protected from being washed away by the urine flow. *In vivo* studies in pigs have supported this hypothesis. The examined crystals had similar compositions but were of different sizes and had differing chemical and physical properties (Fig. 5).

Examining the urine microbiome can also give further insights into biofilm formation and catheter-associated problems through identifying the commensal and residential bacteria of the urinary tract. Individual patient microbiome analysis can further be used for the prognosis of potential clinical problems. However, this only applies to patients with bacteriuria as normally urine is thought to be sterile. With bladder catheterization, there is a high risk of contamination with urethral bacteria which can mask the signals from the residential microbiota [62].

Buhmann et al. examined several urine microbiota from encrustations on ureteral stents with a combination of complementary methods in patients without urinary tract infections or bacteriuria [63]. With real time PCR (qPCR) it was possible to quantitatively estimate bacterial numbers in encrustations, and next generation sequencing (NGS) of the 16S-rRNA gene was used to identify bacterial DNA. It was shown that the insertion of a ureteral stent for up to 6 weeks was associated with a lower bacterial colonization of the encrustations. In patients without clinically
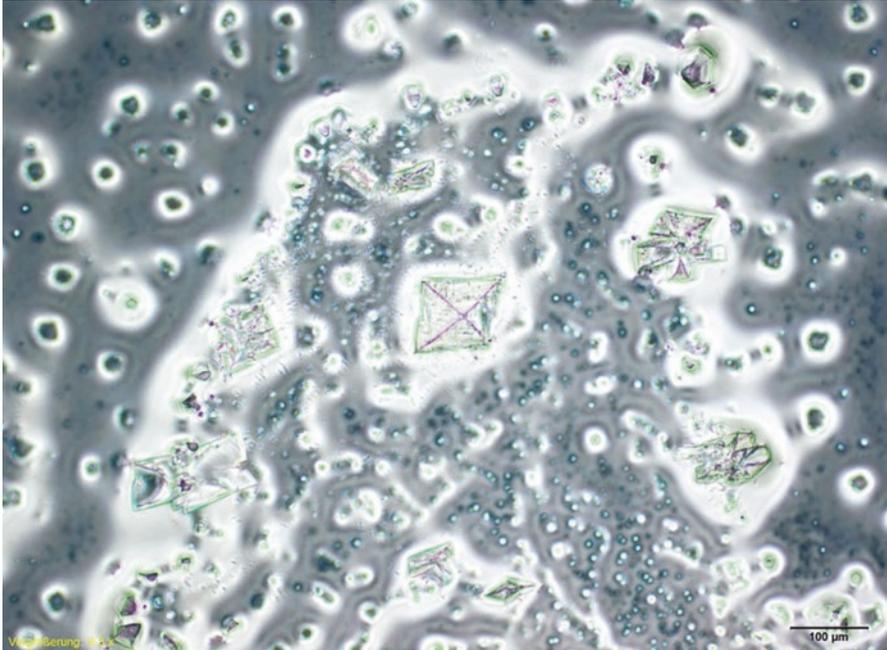
Fig. 5 Induced crystal formation in the pig model: precipitates of calcium oxalate in urine. The crystals have different sizes as well as different chemical and physical properties. Calcium dihydrate (weddellite), calcium monohydrate (whewellite): small crystals with dumbbell shape or envelope shape. BX43—phase contrast lens UPLSAPO 2 40×/0.95, Olympus

relevant urinary tract infections facultative pathogenic bacteria seem to be predominant.

The identification of bacteria with MALDI-ToF MS (matrix-assisted laser desorption ionization-time-of-flight mass spectrometry) is currently used in combination with other technologies to increase the scope of relevant analyses. MALDI-ToF MS can be used for the fast identification of bacteria in encrustations without prior culture or subculture [64]. However, for the identification of bacteria in urine microbiological culture and selective identification of bacteria are still required [65].

6   Conclusions

Crystallization processes in urine, bacterial adherence and encrustation of biomaterials in the urinary tract are usually the result of a multifactorial process with an interplay between many physicochemical and biochemical processes. While all non-infectious urinary stones and encrustations develop on the basis of metabolic, endocrine or renal disturbances, the presence of bacteria in the urinary tract, especially of those producing urease and their enzymatic activity, increases the urinary

pH. This changes the solubility product of calcium and magnesium salts which, in turn, facilitates encrustations.

Taken together, the use of urinary implants is characterized by three interrelated problems:

a tendency for encrustations through the deposition of urinary crystal-forming ions, facilitation of bacterial colonization and persistence despite antibiotic prophylaxis/
    treatment, and
mechanical irritation with resulting reaction of the ureteral tissues.

Coated catheters which potentially could minimize the risk of a complicated urinary tract infection and could allow for longer indwelling times without complications are to date not recommended by urological guidelines [66, 67].

Work is underway for new concepts to develop biomaterials with reduced encrustation propensity and biofilm formation. Promising candidates are coated materials with anti-adhesive properties through covalent binding, high hydrophilicity, and good mechanical properties allowing for adequate patient comfort. For urinary tract catheters with an in-dwelling time under 6 weeks, self-absorbing biomaterials might be a good solution.

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