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A Review of Pathological Biomineral Analysis Techniques and Classification Schemes

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1. Introduction

The skeleton and teeth are mineralized tissues in the human body. We describe them as physiological biominerals. The origin of them is connected with a precise function in the human body.

In addition to these, there are also biomineralizations occurring spontaneously in the human body, giving rise to disease. These biomineralisations are called pathological biominerals. Urinary stones are an example.

Urinary stones can be composed of an organic matrix mainly containing proteins, lipids, carbohydrates and cellular components, and biominerals.

The compositional analysis of urinary stones is an important requirement for a successful management of the disease, which implies not only a proper evaluation and treatment, but also prophylaxis to prevent recurrence, which is impossible without knowing the composition of the urinary stones involved.

This is a brief review and a comparative study of the principles and practical application of various chemical and physical techniques used for urinary stone analysis.

The different methods for classifying and grouping urinary stones by results of analytic techniques are also compared and evaluated.

2. The pathological biominerals

The term biomineral refers not only to a mineral produced by organisms, but also to the fact that almost all of these mineralized products are composite materials comprised of both mineral and organic components. Furthermore, having formed under controlled conditions, biomineral phases often have properties such as shape, size, crystallinity, isotopic and trace element compositions quite unlike its inorganically formed counterpart.

Biominerals meet the criteria for being true minerals, but they can also possess other characteristics that distinguish them from their inorganically produced counterparts. The

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most obvious trait is that biogenic minerals have unusual external morphologies. It is perhaps the intricacy and diversity of bio-originated structures that first attracts mineralogically-inclined persons into the field of biomineralization.

A second characteristic of biominerals is that many are actually composites or agglomerations of crystals separated by organic material. In many organisms, they exist as small bodies distributed within a complex framework of macromolecular frameworks such as collagen or chitin (Addadi et al., 2003).

Biominerals can be classified on the same framework as minerals, by composition based on the anionic constituents.

The phenomenon of biomineralisation has been well known for a long time, but insufficiently investigated up to now (Epple, 2002).

The processes of mineralisation in the human body in normal conditions occur in bones and teeth. Bone is the hard connective tissue that forms the skeleton of vertebrates. It consists of layered organized fibrils of collagen impregnated with calcium phosphates containing carbonates and small amounts of other ions, which compose the mineral part of the bone and constitute 60–70% of its weight.

Bones and teeth protect the internal organs, allow enhanced mobility, enable mastication of food, perform other mechanical functions, and are a ready source of the key regulatory inorganic ions calcium, magnesium, and phosphate. The sizes and shapes of bones reflect their function.

The processes of mineralisation in the human body produce also pathological biominerals like arteriosclerosis and kidney or urinary stones.

Formation of crystals in pathological mineralizations follows the same principles as normal calcifications. Local conditions for nucleation require a certain degree of local supersaturation induced by biochemical processes, which can be promoted by deficiency of inhibitors (like diphosphate, magnesium or even citrate ions) and/or the presence of matrix of organic material (such as cholesterol) or other crystals of different solids, that act as heterogeneous nuclei.

While apatite structure minerals are the solid phases found in normal mineralized tissues, pathological calcifications contain several solid phases.

2.1 Urinary stones

Renal lithiasis (renal calculi) affects a wide sector of population, between 4 and 15% approximately (depending on geographical area), and it has been classified as one of the illnesses that can cause much pain to human beings.

Calculi are often heterogeneous, containing mainly oxalate, phosphate, and uric acid crystals. The sequence of events that triggers stone formation is not fully understood yet.

Urinary stones are located in the kidneys, and only a small percentage is lodged in the urinary bladder and urethra.

Kidney stones less than 5 mm in diameter have a high chance of being passed, while those of 5–7 mm have a 50% chance, and those over 7 mm almost always require urological intervention. Renal colic (flank pain) develops as the stone begins its passage down the urinary tract. While approximately 90% of stones are successfully passed out of the urinary tract, the remaining stones generally have to be surgically removed by ureteroscopy or percutaneous nephrolithotomy or comminuted by the non-invasive technique, shock wave lithotripsy.

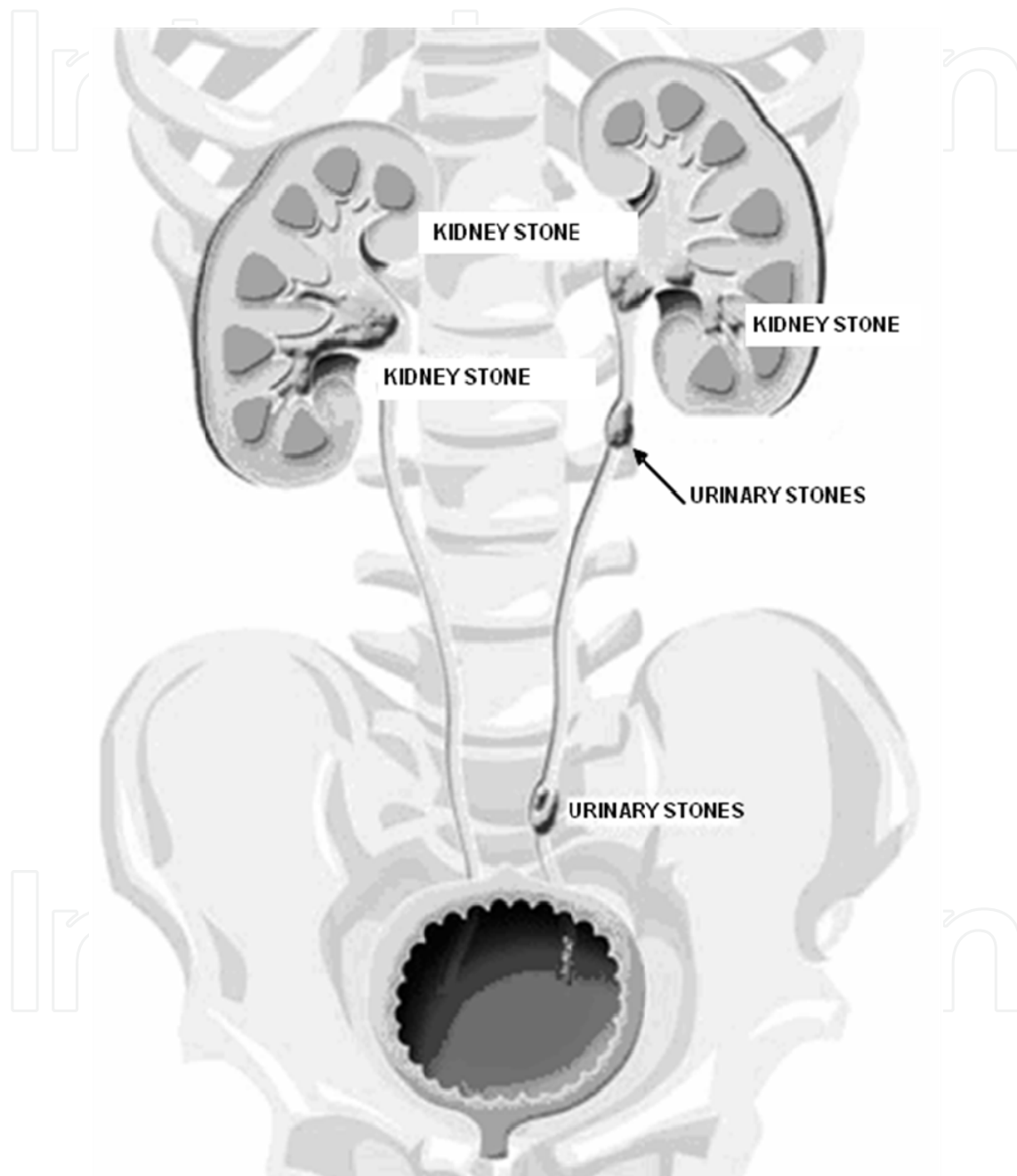


Fig. 1. Urinary and kidney stone localization

General conditions that contribute to stone formation include, e.g., a high concentration of salts in urine, retention of these salts and crystals, pH, infection, and a decrease in the body's natural inhibitors of crystal formation (fig. 2).

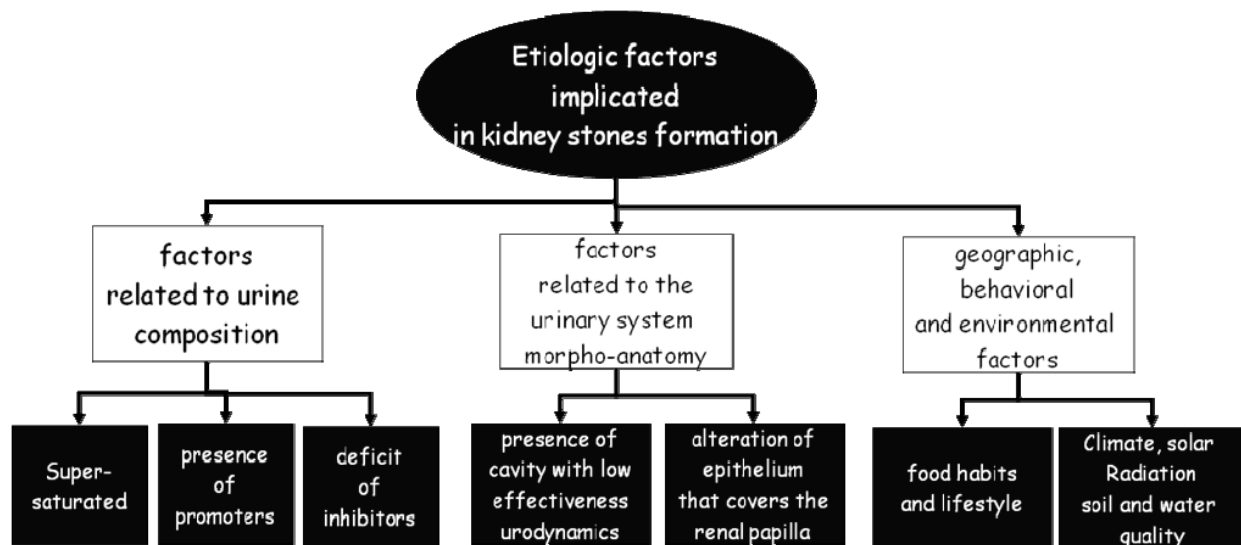


Fig. 2. Etiological factors implicated in kidney stones formation

Many pathways can lead to increased urinary supersaturation. As one example, increased calcium oxalate supersaturation may result from low urine volume or excessive excretion of calcium or oxalate, or combinations of these factors. Hypercalciuria and hyperoxaluria can be result from interaction of genetic susceptibility and environmental triggers, in varying proportions.

Modern medical treatments for stone prevention are largely based on methods to decrease supersaturation effectively, and, thus, doctors are most interested in the pathophysiology leading to specific types of supersaturation.

2.1.1 The minerals inside

The composition of kidney stones can be classified into two parts. The first part is represented by organic matrix containing mainly proteins, lipids, carbohydrates, and cellular components. The other part is biomineral component.

There are some examples of crystalline drug-induced stones that include: indinavir monohydrate, atazanavir sulfate, ceftriaxone (as calcium ceftriaxonate), N4-acetylsulfadiazine, N4-acetylsulfamethoxazole, amoxicillin trihydrate, and triamterene (Schubert, 2000; Dao & Daudon, 1997).

Quartz, calcite, gypsum, and seedcorns are found as artefacts or falsifications among others.

A majority of kidney stones are calcium stones, with calcium oxalate (CaOx) and calcium phosphate (CaP) accounting for approximately 80% of all of these stones, uric acid (UA) about 9%, and struvite (magnesium ammonium phosphate hexahydrate, from infection by bacteria that possess the enzyme urease) approximately 10%, leaving only 1% for all the rest (cystine, drug stones, ammonium acid urate).

Calcium oxalates crystallize has three hydrates— calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (also known as weddellite) (Sterling 1965; Tazzoli and Domeneghetti 1980), and calcium oxalate trihydrate ($\text{CaC}_2\text{O}_4 \cdot 3\text{H}_2\text{O}$; COT) (Deganello et al. 1981), a less common form in pathological stone formation.

Chemical name	Mineral name	Chemical formula	Abbreviation
Oxalates • Calcium oxalate monohydrate • Calcium oxalate dihydrate	Whewellite Weddellite	$\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$ $\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$	COM COD
Phosphates • Calcium phosphate • Calcium hydrogen phosphate • Magnesium ammonium phosphate hexahydrate	Hydroxyapatite Brushite Struvite	$\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ $(\text{NH}_4)\text{Mg}(\text{PO}_4) \cdot 6\text{H}_2\text{O}$	HA BR STR
Purines • Uric acid • Monosodium urate monohydrate		$\text{C}_5\text{H}_4\text{N}_4\text{O}_3$ $\text{NaC}_5\text{H}_3\text{N}_4\text{O}_3 \cdot \text{H}_2\text{O}$	UA MSU
Other • L-Cystine		$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2$	CY

Table 1. Mineral components of urinary calculi

COM and COD crystals are readily distinguished by their crystal habits (fig. 3): COM usually exhibits hexagonal lozenge morphology, but COD crystallizes as bipyramids, reflecting its tetragonal crystal point group symmetry.

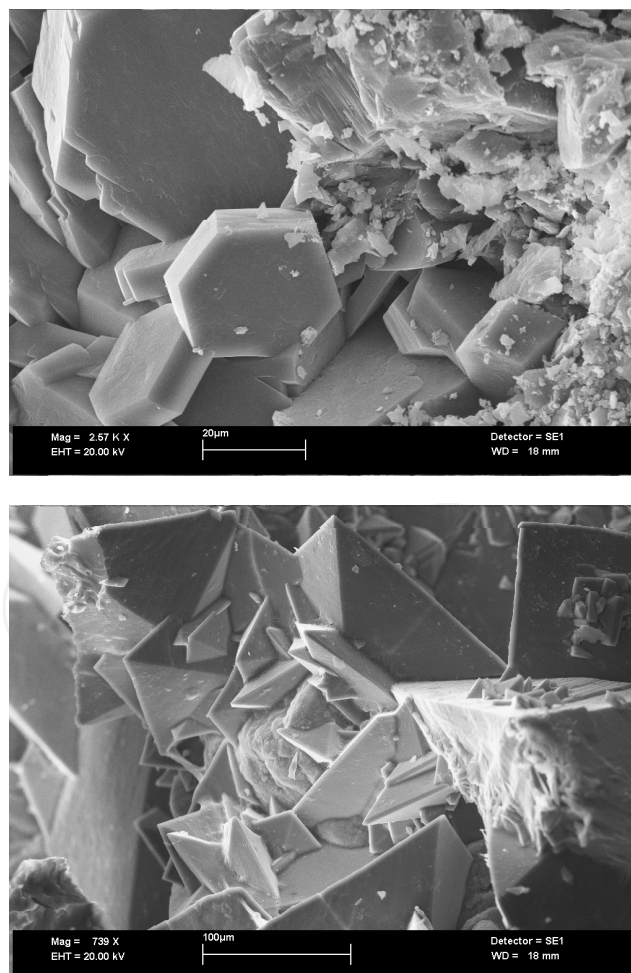


Fig. 3. Calcium oxalate monohydrate and calcium oxalate dihydrate crystals at Scanning electron microscopy view

Sometime stones are made of a single large weddellite crystals (fig. 4), in other cases entire weddellite crystal are transformed into whewellite the most thermodynamically stable form (fig. 5) (Grases et al., 1998).

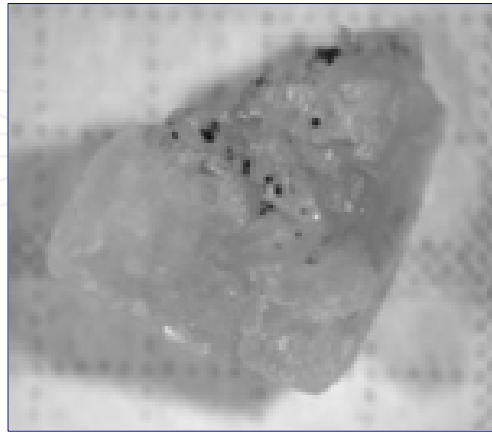


Fig. 4. Weddellite single crystal labelled "spearhead" at stereo-microscopy

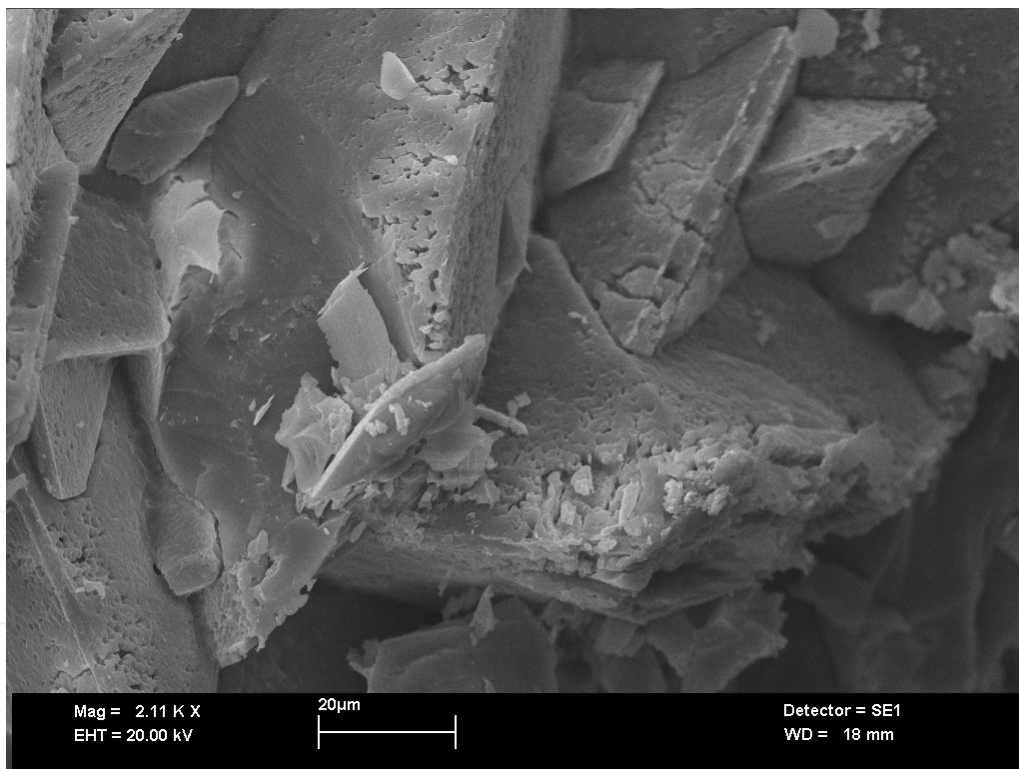


Fig. 5. Weddellite transformation in whewellite, photo at SEM

Various calcium phosphate crystal phases (fig. 6) occur in about one-third of stones, with apatite (apatite is a general term for calcium phosphate in which various anions, e.g. carbonate, fluoride, hydroxide, and chloride, are partially substituted) and brushite found most often admixed with calcium oxalate in an individual stone.

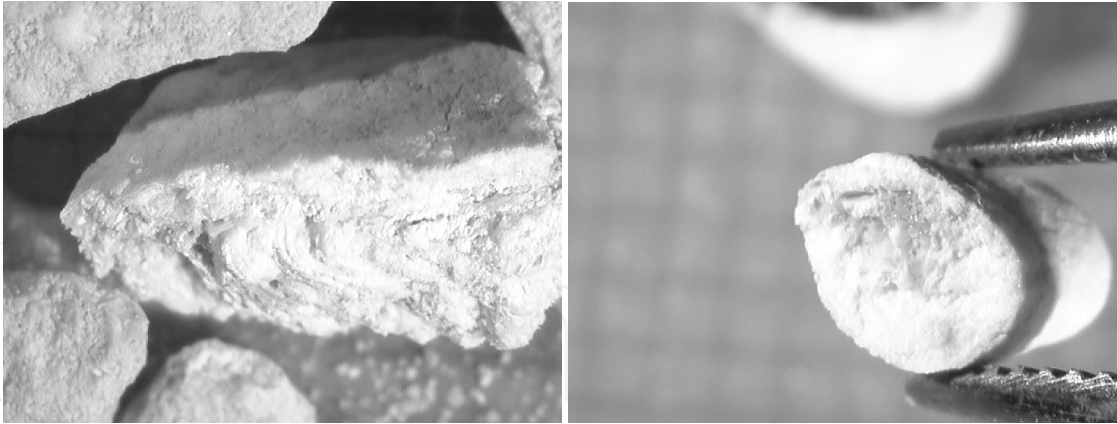


Fig. 6. Phosphates stones at stereo-microscopy observation

Struvite, another mineral entirely constituting some of the stones analyzed, belongs to the group of phosphate so it was difficult to recognize the single struvite crystals at the stereo-microscope, because they appear white and look similar to the other minerals of the same group. Struvite stones are recognizable thanks to their large size and coral form (fig. 7). Despite their porosity, these stones were among the heaviest samples (average weight 155mg).

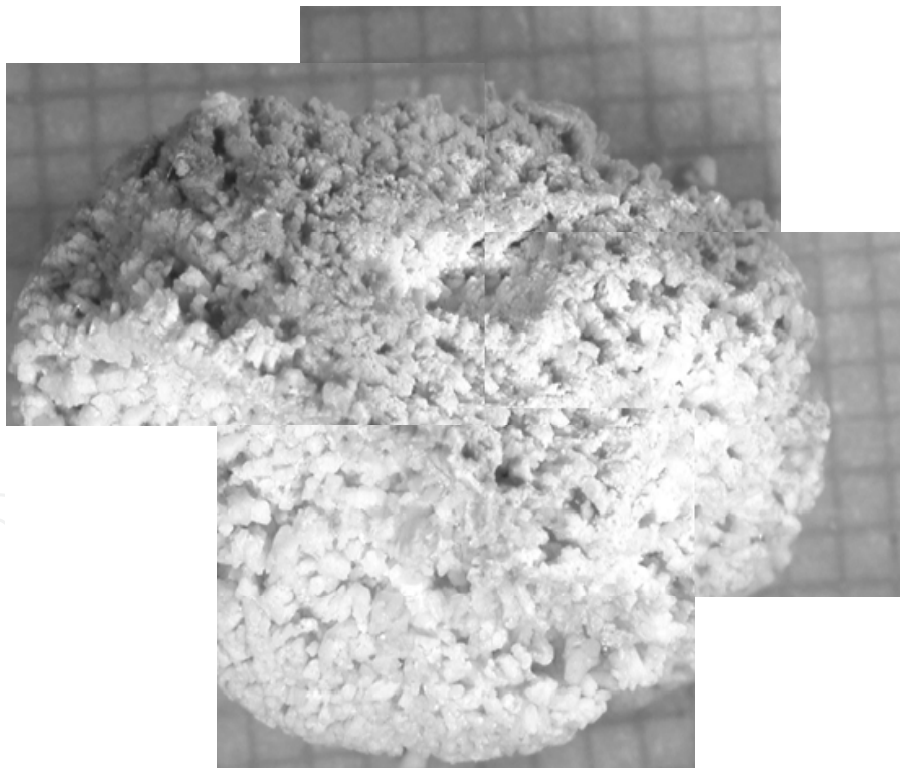


Fig. 7. Struvite stone at stereo-microscopy observation

Cystine stones (fig. 8) are easily recognizable for their appearance: round form and yellow wax colour. The crystals are recognizable by SEM and in thin section by their hexagonal shape. For this type of samples a compact internal structure without porosity was recognized.

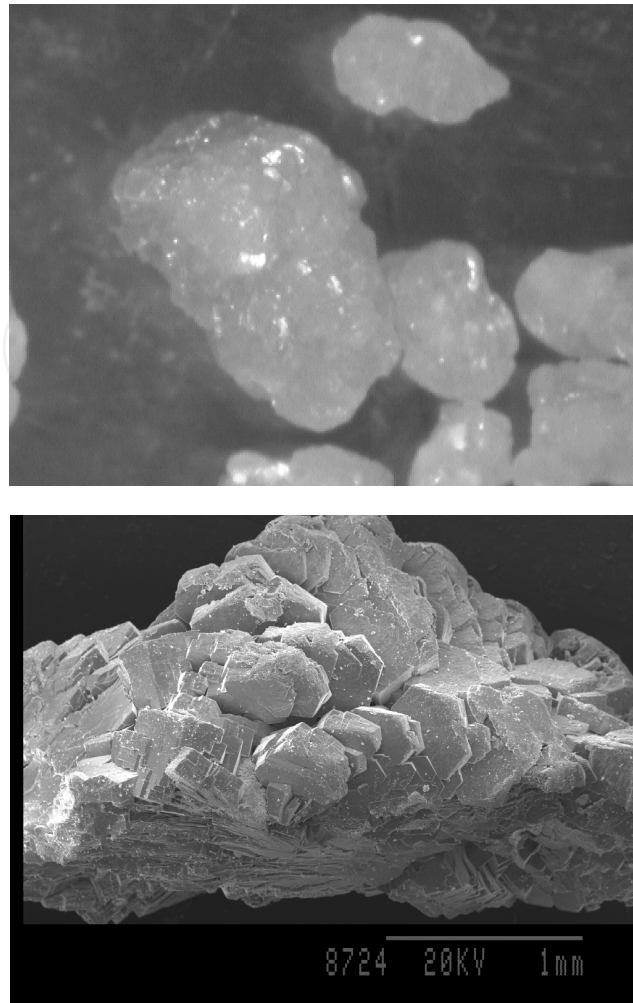


Fig. 8. Cystine at stereo-microscopy and SEM observation

Different types of uric acid crystals (fig. 9) are found in about 10% of stones and are frequently combined with calcium oxalates.

Uric acid monohydrate is very rare, and recently described by the author for the first time (Schubert et al., 2005). The very rare occurrence of a second form of uric acid (Schubert, 1995) could be confirmed by the author. Ammonium urate has a frequency of 1%. The other urate and purine derivatives, such as xanthine and dihydroxyadenine, are absolutely rare.

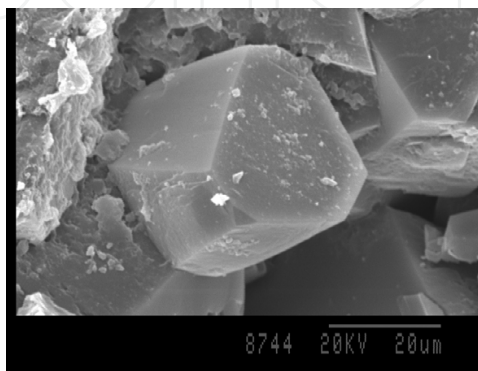


Fig. 9. Uric acid crystals at SEM

3. Techniques for the characterization of kidney stones

Over the first three decades of this century, the stone chemical composition has been investigated only with qualitative methods. These kind of analyses implied wet chemistry qualitative reactions in order to identify the different anions and cations present in the urinary stones. Often this examination is still carried out in the routine clinical laboratory by using specifically designed kits.

More recently, the dissolution of the stones in acidic solution and quantitative measurements of different ions have been performed by atomic absorption spectroscopy or atomic emission spectroscopy with inductively coupled plasma. Many investigators have appreciated the value of quantitative chemical analytic techniques, and several schemes for the classification of urinary stones have been suggested.

On the contrary, in the nineties as for urinary stone analysis there have been a progressive increase in the use of physical techniques (i.e., infrared spectroscopy and X-ray diffraction) and a decrease in the use of chemical methods which by now are regarded as unsatisfactory.

A progressive increase in the use of infrared spectroscopy technique in various biochemical laboratories is observed as it defines the stone composition with accuracy.

This is expected to make procedures easier, revealing more detailed information on mineral structure and the possible identification both of stone type and biomineralisation site.

The X-ray diffraction and crystallographic techniques of polarization microscopy are useful tools in the study of the crystalline structure, order of deposition of components and the nucleus of the urinary stones.

Optical observations can be carried out with a stereomicroscope to determine colour, shape, overall appearance, surface features and any possible occurrence of crystalline layers and/or organic matter on the surface, but the results are only qualitative.

The micro- X-ray analysis which uses an X-ray micro-diffractometer is the most advanced technique. It can be used for classifying urinary calculi by composition as it can detect the multiple stone components and show its structural arrangement, on a whole stone without fragmentation.

Methods of urinary stone analysis			
	Type of information		
	Chemical composition	Mineralogical composition	Texture
Chemical analysis	full	limited	
Thermal analysis	limited	limited	
SEM	full	limited	full
X-ray diffraction		full	
Infrared spectroscopy		full	
Polarization microscopy		limited	full

Table 2. Methods of urinary stone analysis and their potential information

So far no method has been found to be suitable for providing all the useful information on the structure and composition of urinary stones (tab. 2), only a combination of a refined morphological and structural examination of stones with optical and scanning electron

microscopy, completed with a compositional analysis by using X-ray powder diffraction, can provide a precise and reliable method for the identification of the stone type.

3.1 Chemical methods

The chemical method can identify fairly small amounts of an element but cannot usually identify a compound as such, and in stones of mixed composition, the results merely indicate which ions and radicals are present.

Some of the basic principles (Sutor et al., 1971) of this kind of analysis are the follows:

- A little powdered stone is acidified with 15N hydrochloric acid. Liberation of carbon indicates the presence of carbonate;
- Addition of 20% sodium acetate. A white precipitate indicates the presence of oxalate;
- Addition of ammonium molybdate and 1-amino-2-naphthol-4-sulphonic acid solution. A blue colour shows the presence of phosphate;
- Neutralisation with 5N sodium hydroxide alone. If a white precipitate occurs subsequent addition of 4-nitrobenzene-azo-resorcinol produces a blue colour in the presence of magnesium and a pink colour in the presence of calcium;
- Neutralisation with 5N sodium hydroxide, addition of 15% sodium cyanide and then addition of Folin's uric acid reagent. A blue colour indicates the presence of uric acid;
- Alkalinisation with 5N sodium hydroxide, addition of 15% sodium cyanide and then freshly prepared sodium nitroprusside. A deep purplish colour is obtained in the presence of cystine;
- Neutralisation with 5N sodium hydroxide and addition of Nessler's reagent. A yellow brown colour is formed in the presence of ammonia.

Unfortunately, chemical methods are destructive and need several milligrams of the sample, so small stones cannot be analyzed with chemical methods.

Qualitative and semiquantitative chemical analysis is not accurate and can lead to clinically significant errors (Silva et al., 2010; Westbury, 1989).

Chemical analysis detects calcium and oxalate separately and therefore cannot differentiate crystalline types of CaOx. In a study, COM and COD were evenly distributed (32% each) (Silva et al., 2010). In cystine-containing stones identified by chemical analysis, urate was a major component while cystine was a minor component; however, in the morphological analysis, cystine was a major component. This suggests cystine stones may easily be confused with urate stones if submitted to chemical analysis only.

Currently, chemical analysis of the stones are still practiced but with other methods such as X-ray fluorescence (XRF) spectroscopy and atomic absorption spectroscopy (AAS) or more advanced methods such as SIMS (secondary ion mass spectrometry) (Ghumman et al., 2010).

The most widely practiced chemical analysis, however, are those aimed at identifying not only major elements but minor and trace ones (Trinchieri et al., 2005; Moe, 2006; Atakan et al., 2007; Bazin et al., 2007; Joost & Tessadri, 1987; Meyer & Angino, 1977; Munoz & Valiente, 2005; Sutor, 1969; Welshman & McGeown, 1972). The latter may have played a significant role in urinary stone nucleation and growth, or may be considered as environmental pollution markers (ATSDR, 2008; Bernard, 2008; IPCS, 1992; Jarup, 2002; Patrick, 2003; Satarug et al., 2010).

The major and minor constituents of stones can be investigated by Laser-induced breakdown spectroscopy. The first report, appeared in the literature, on the analysis of biliary stones by LIBS was Singh et al. (2009).

Atomic emission spectroscopy (AES), inductively coupled plasma (ICP), atomic absorption spectroscopy (AAS), neutron activation analysis (NAA), proton-induced X-ray emission (PIXE), and X-ray fluorescence (XRF), require time and labor-intensive specialized sample preparation and presentation protocols for the analysis of elemental composition (Al-Kinani et al., 1984; Zhou et al., 1997).

For fast and in situ analysis, LIBS has been found to be a suitable technique for elemental analysis of any kind of materials (Rai et al., 2002, 2007). The advantage of the LIBS technique is that it does not require any special sample preparation and presentation efforts.

The LIBS technique has proven its own clinical significance for other in vivo applications such as in dental practice for the identification of teeth affected by caries (Samek et al., 2000, 2001). Kumar et al. (2004) have demonstrated LIBS experiments to explore the possibility of using LIBS for in vivo cancer detection.

3.2 Optical and Stereoscopic Microscopy

Binocular stereoscopic microscopy (BSM) is an easily applicable, cost-efficient tool, used to obtain accurate and reliable information regarding the stone components.

Many constituents of renal calculi may be recognized on sight when examining the fractured surfaces under a binocular stereoscopic microscope, permitting a guess as to the probable majoritary composition of the stone.

In practice, the method permits to distinguish between calcium oxalate and calcium phosphate stones. Cystine stones commonly consist of aggregates of well-formed hexagonal prisms or hexagonal tablets and it is very easy to diagnose them with BSM.

BSM was not successful in the analysis of struvite stones.

The analysis of stone composition with microscopic inspection (including polarizing microscopy) is very inaccurate and unfortunately too frequently used for the routine analysis of stones (Herring, 1962; Brien et al., 1982; Prien, 1963). This technique is not capable of identifying small amounts of crystalline materials in admixed samples. A significant contribution to the potentially low level of accuracy using this method is that the accuracy is entirely dependent on the level of sophistication and experiences of the technicians conducting the analyses (Prien, 1963; Silva et al., 2009).

The clinician can perform BSM himself. We believe that any doctor with practical experience can learn to perform an investigation of this kind in a short time. The shape and colour of the stone may provide important information. Following fracturing of the calculus, the order of deposition of components is determined, including identification of an apparent nidus and other patterns, whether homogeneous or characterized by layered, concentric, or radial deposition.

Moreover, what is even more important during BSM analysis is the internal inspection of sections for identifying several structural features, such as the degree of internal organization, the location and size of the nucleus of the stone, the presence of lamination

and/or radial structure in the bulk of the stone, the order of deposition of the components when lamination is present and other structural details.

Likewise, it is possible to distinguish between a sedimentary calcium oxalate monohydrate stone, which shows little or no regularity of the central structure but an outer layer of perfectly developed columnar crystals, and a calculus of the same composition developed by crystal growth which shows a perfectly arranged internal structure.

Some of the best work on the architecture of stones has utilized thin sections of stones, which are studied by optical methods (Murphy & Pyrah, 1962; Cifuentes, 1977). Such studies have elegantly shown the nature of the progressive addition of layers to stones, and have also attempted to identify the nucleus, or initial nidus of the stones (Jung-Sen Liu et al., 2002; Sokol et al., 2003).

The majority of these studies have employed transmission methods of analysis, which require the sample to be present as thin sections approximately 6 μ m thick (Ouyang et al., 2001; Paschalis et al., 2001; Gadaleta et al., 1996; Mendelsohn et al., 1999, 2000). Unfortunately, thin sections of reproducible thickness are difficult to obtain with urinary stones because of the fragile nature of the material (Murphy & Pyrah, 1962; Cifuentes, 1977).

3.3 Scanning Electron Microscopy (SEM)

Electron microscopy is another method for ultramicroscopic investigation of the fine structure of urinary stones, including single crystal surface structure, sections of urinary calculi, and the possible presence of unknown components within the calculus (Hesse et al., 1981; Hyacinth et al., 1984). However, it also needs specialized equipment. The material in urinary calculi is also prone to irradiation damage during electron microscopy and this suggests the need for care in the interpretation of data (Crawford, 1984).

Scanning electron microscope uses electrons rather than light to form an image (Walther et al., 1995). It has a large depth of field, which allows a large amount of the sample to be focused at a time. SEM produces images of high resolution, which means that closely spaced features can be examined at a high magnification (Harada et al., 1993). Preparation of sample is relatively easy since most SEMs only require the sample to be conductive (Lee et al., 2004). The spatial distribution of major and trace elements can be studied in a range of human kidney and bladder stones with well-documented histories to understand their initiation and formation

3.4 X-ray diffraction analysis

There is no doubt that XRD is the most-appropriate method to determine mineral structures. XRD can distinguish all the different crystal types in a particular mixture, and is therefore accepted as the gold standard for stone analysis (Ghosh et al., 2009; Giannossi et al., 2010). However, this method is not easily accessible. Furthermore, it is expensive, requiring specialized equipment and trained staff.

XRD has advantages of reliability in qualitative analysis and accuracy in quantitative analysis. It operates simply and has a high sensitivity. Based on XRD diffraction data, the multicomponents in a sample can be measured simultaneously.

Another advantage of the X-ray powder diffraction technique is that the powder can be characterized without a surgical procedure by analyzing the fragmented crystals collected from the urine, which follows the extra-corporeal shock wave lithotripsy ECSWL.

Virtually all crystal structures are unique in some structural aspect and their diffraction patterns can be differentiated from other structures and diffraction patterns (fig. 10). Highly sensitive and accurate XRD instruments are often necessary to differentiate some of the structures seen in stones as their chemistry and crystal structures can be similar.

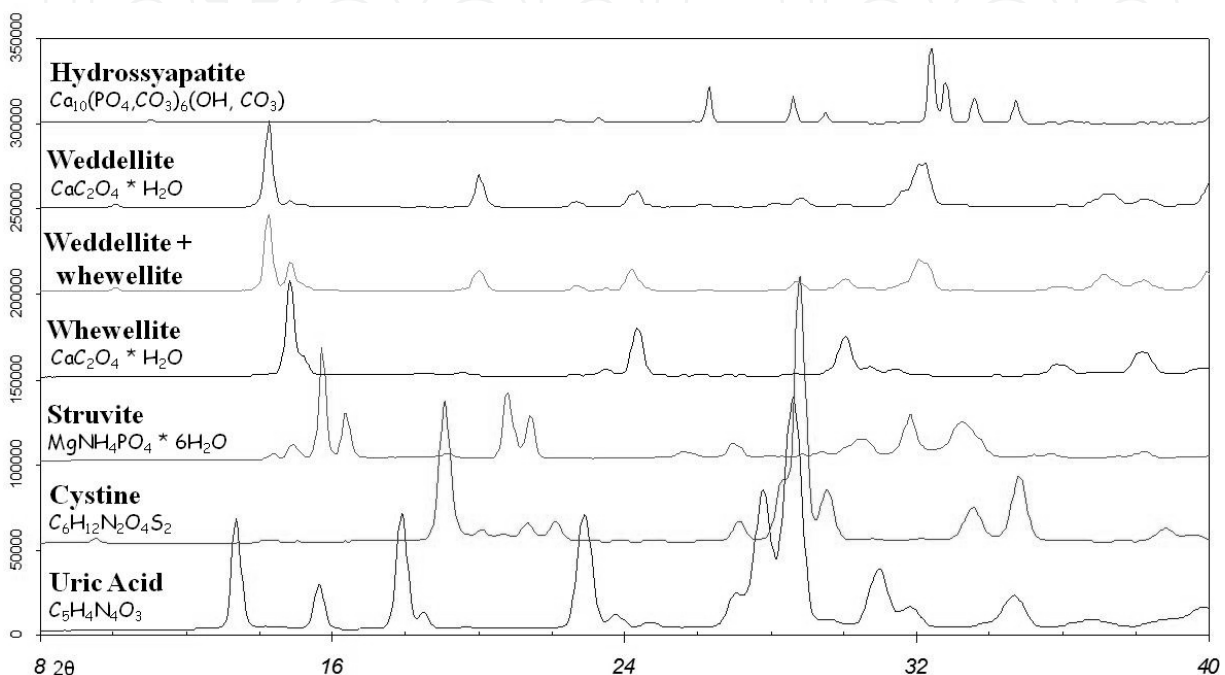


Fig. 10. XRD profiles

The XRD data for the most common components of human kidney stones are presented in Table 3.

COM		COD		AP		ST		UA		CY	
d (Å)	I	d (Å)	I	d (Å)	I	d (Å)	I	d (Å)	I	d (Å)	I
5.93	100	8.70	12	8.15	29	5.90	38	6.56	38	4.70	100
5.79	25	6.31	100	5.26	6	5.60	45	5.63	20	4.68	100
4.64	7	6.15	45	4.08	8	5.38	22	4.91	48	4.63	100
4.52	6	4.40	45	3.89	10	4.60	6	4.76	6	4.45	5
3.78	13	3.89	14	3.44	45	4.25	100	3.86	55	4.20	7
3.65	100	3.09	18	3.17	10	4.14	34	3.70	5	3.32	8
3.00	10	3.07	18	2.81	100	3.29	24	3.28	14	3.18	19
2.97	46	2.81	20	2.78	62	3.02	10	3.18	70	3.13	30
2.91	12	2.77	20	2.72	58	2.96	16	3.09	100	3.06	16
2.89	10	2.75	85	2.63	31	2.92	46	2.87	25	2.71	16
2.84	14	2.41	14	2.53	5	2.80	26	2.80	10	2.70	32
2.48	30	2.39	14	2.40	7	2.72	8	2.57	18	2.68	32
2.34	90	2.33	10	2.26	20	2.69	37			2.60	17

Table 3. XRD data for the most common components of human kidney stones

The diffraction data are presented in crystallographic language as interplanar d-spacings in Ångstroms ($d(\text{Å})$) associated with the distances between atoms in the structure and as diffraction intensities either relative to a weak versus strong scale or on a maximum of 100 scale (Sutor et al., 1968; Mandel & Mandel, 1982; JCPDS, 1985).

In practice, the experimental XRD patterns are compared with those for the standard patterns presented in Table 3. All diffraction lines of a given standard pattern, especially the strongest lines, must be matched with diffraction lines in the sample pattern. If some lines of a given intensity are thought to match a standard, then all lines with equal or greater intensity must also match the standard lines. Remaining unmatched lines are used to determine any other crystalline components in the sample. With the advent of high resolution XRD cameras utilizing focusing monochromators and high flux X-ray generators, the ability to detect minor stone components has greatly increased as the diffraction patterns appear sharper and diffraction lines are easily differentiated from neighbouring diffraction lines separated by as little as 0.01–0.03 Å interplanar spacings.

Renal calculi with calcium oxalates are represented by the general formula $\text{CaC}_2\text{O}_4 \cdot x\text{H}_2\text{O}$, where x is the number of bonded-water molecules, which can vary from 1 to 2. It can be formed on crystalline seed particles of organic or inorganic compounds that work as a nucleating substrate. Therefore, the H_2O molecule might be bound or free, depending on if the H_2O molecule belongs to the crystal structure or the organic compound among them. Some of the characterization techniques commonly used are not suitable to give the structural information about the H_2O molecule.

The increased sensitivity has allowed for the identification of smaller amounts of poorly crystalline materials such as apatite. Unfortunately, if the stone material is a drug, or drug metabolite whose XRD pattern or single crystal structure has not been published, XRD methods fail to definitively characterize the sample. In those cases, the XRD method can only tell you what the stone is not composed of.

Many modern methods of analysis, also powder XRD, destroy the structure of the calculi when the samples are prepared for introduction into the instrument. Maintaining the structural integrity of the calculi is important for the elucidation of the chemistry of formation and the etiology of the calculi in the urinary system.

The micro-diffractometer XRD is preferable used when a very limited amount of sample is available but also on the bulk sample, without any type of treatment.

3.5 Fourier Transform Infrared (FT-IR) spectroscopy

Several reports have been published on the comparison of IR techniques to wet chemical methods for renal stone and other biological analysis, though these can be somewhat outdated (Anderson et al., 2007; Gault et al., 1980; Carmona et al., 1997).

Infrared spectroscopy was first applied to stone analysis by Beischer in the mid fifties (1955).

Weissman et al. (1959), Klein et al. (1960), Tsay (1961), Takasaki (1971), and Modlin (1981) have performed analysis of renal stones by IR with paste and KBr table method. Bellanato et al (1973) have identified with IR the different types of oxalates, phosphates and urate in urinary stones. Oliver and Sweet (1976), proposed a systematic scheme for the qualitative identification and interpretation of the IR spectra which was applied by Gault et al. (1980),

and compared with wet chemical analysis. It is a useful technique for identifying organic and inorganic compounds. In fact, it is particularly useful for determining functional groups present in a molecule, because they vibrate at nearly the same frequencies independently on their molecular environment.

Like X-ray diffraction, infrared spectroscopy provides results on the actual salts, including the different degree of hydration, with an additional advantage of identifying non crystalline compounds, whereas X-ray diffraction cannot. Moreover, recent advances in computerized infrared spectroscopy, particularly Fourier transform infrared (FT-IR) spectroscopy, have allowed to obtain infrared spectra in less than a minute, whereas in a conventional X-ray apparatus each run requires some hours. Finally, the quantity of sample needed for Fourier transform infrared spectroscopy can be less than one microgram.

In FTIR spectral analysis, spectral data is related to the vibrational motions of atoms in bonds (e.g., bond stretching, bond contracting, or bond wagging, etc.).

Classically, the powdered sample is admixed with powdered potassium bromide, compressed into a nearly transparent wafer, and the IR beam is passed through the wafer. Recently, advances in other sample preparation methods have allowed powdered samples to simply be ground to ensure optimal sampling of a multicomponent stone and then the IR beam is directed at the sample surface (attenuated total reflectance). Although FT-IR can yield qualitative and quantitative results, the preparation of the calculi samples is time consuming and difficult.

The reflected IR beam containing spectral data specific to the sample is then recorded.

The IR pattern contains absorption bands representing specific energies (presented as wavelengths in units of cm^{-1} , or more commonly known as wavenumbers) corresponding to molecular motions in molecules. It is therefore possible to differentiate molecular motions in similar organic groups. The IR pattern of a mixed component stone is frequently very complex, but the advent of computer controlled IR spectrometers, especially modern FTIR spectrometers has allowed for computer assisted pattern stripping and comparative standards library matching.

For XRD and FTIR, the accuracy of the analysis is very strongly dependent on the quality of standard spectra. Most laboratories conducting stone analyses prepare their own standards libraries. Unfortunately, many analysis laboratories use patient stone material to create their standard spectra. As their stones are analyzed by the same method as they are using to analyze other stone samples, their unknowns become their standard. As virtually no stone is composed of only one pure crystalline component, such spectral libraries are very inaccurate and the potential for skewed and inaccurate stone analysis is highly probable. Preparation of synthetic stone components for the generation of standards and verification of composition by alternative methods is the only correct way to prepare a standards library for either XRD or FTIR, especially for FTIR. Commercial libraries should only be used for supplemental data in those rare instances when experimental data cannot be correlated with defined stone component standards, especially for identification of nonbiologic or false stones.

Identification is very simple if a reference spectrum that matches that of the unknown material is found. When an exact reference spectrum match cannot be found, a band by band assignment is necessary to determine the composition of the solid.

Infrared spectroscopy permits to clearly distinguish between a calcium oxalate monohydrate renal calculus and a calcium oxalate dihydrate renal calculus. Thus, absorption bands comprised between 3500 cm^{-1} and 750 cm^{-1} are clearly different for both compounds (Daudon et al., 1993).

All phosphate containing calculi show an intense absorption band around 1000 cm^{-1} . This band permits its easy identification even in mixtures with calcium oxalate monohydrate or dihydrate. Pure brushite calculi are not frequent, but they exhibit characteristic IR spectra that allow to clearly distinguish them from hydroxyapatite or ammonium magnesium phosphate calculi.

Uric acid is probably one of the cases where a wider variety of sizes and colours can be found, and consequently important mistakes can be produced if the identification is exclusively performed visually. The infrared spectra of such calculi are, nevertheless, characteristic and permit their easy identification without any difficulty and also allow their clear differentiation from the infrared spectrum corresponding to ammonium urate calculi due to the different absorption bands comprised between 1300 cm^{-1} and 500 cm^{-1} .

The real benefit of FTIR is the high sensitivity of the new computer controlled spectrometers that can take many repetitive spectra of the same sample and mathematically enhance the sample signal to experimental noise ratio.

3.6 Thermal analysis

The thermal decomposition and structural study of biological materials—urinary calculi (Kaloustian et al., 2002; Afzal et al., 1992; Madhurambal et al., 2009), enamel and dentin (Holager, 1970), and bones (Paulik et al., 1969; Mezahi et al., 2009; Mitsionis et al., 2010)—have been studied many times.

The thermal study of kidney stones has been published (Strates et al., 1969; Ghosh et al., 2009): differential thermal analysis (DTA), thermogravimetry (TG), differential scanning calorimetry (DSC), can, also, characterize the main components (alone or in mixture) in urinary calculi.

When stones are mixtures of the two oxalates hydrates, it is difficult, to differentiate calcium oxalate monohydrate (COM, Whewellite) and calcium oxalate dihydrate (COD, Weddelite) in the binary mixtures, except when one of them is in little quantity in the calculi. A very low heating rate by DSC (0.3 °C min^{-1} , from 100 to 180 °C) permitted the differentiation of the two hydrate forms.

Under nitrogen sweeping, the TG, DTG (derivative curve of the thermogravimetry) and DTA curves of the COM standard, display three typical steps, located in the temperature ranges of about 100 – 220 , 450 – 520 and 600 – 800 °C . In the thermal curves of a calcium oxalate dihydrate sample, two endothermic peaks, attributed to the water volatilization, are near 164 and 187 °C . Then the same curves (DSC, TG) as for COM were observed (Farner & Mitchell, 1963; Berényi & Liptay, 1971).

A simultaneous thermal analysis apparatus (TG-DTA) was usually used, with: heating rate 5 °C min^{-1} , from the ambient temperature to 850 – 1230 °C , gas sweeping: air (0.5 L h^{-1}) or nitrogen (2.5 L h^{-1}). Thermocouples and crucibles were platinum. The sample mass ranged from 3.7 to 10 mg , and kaolin or $\alpha\text{-Al}_2\text{O}_3$ (Merck) was used as an inert thermal reference.

The thermal study can, also, characterize the magnesium ammonium phosphate hexahydrate or struvite, and uric acid (UA).

The average of the peak temperatures, computed from urinary stones of struvite, were, 108 and 685°C. These values are very near those of the struvite standard.

The average temperatures from urinary stones of UA, were 418 and 446°C showing difference with the standards presenting higher values: 429 and 450°C.

3.7 Imaging investigations

The micro computed tomography (micro CT) as a potential method for the analysis of urinary stone composition and morphology in a nondestructive manner at very high resolution (Zarse et al., 2004). Micro CT, which has seen considerable use as a research tool in bone biology (Rueggsegger et al., 1996), has the ability to reconstruct 2-D and 3-D images of urinary stones that allow the 3-D image of the stone to be cut and viewed in multiple planes with voxel sizes of 8–34 μm .

Micro CT allows non-destructive mapping of the internal and surface structure of urinary stones and permits identification of mineral composition based on x-ray attenuation values. Micro CT cannot differentiate mineral types when the stone is highly complex and micro-heterogeneous with significant mixing of different mineral types at a scale below the spatial resolution of the instrument.

4. Type of kidney stones: Classification

Despite the many results achieved with all these techniques, very little attention has been paid to the classification scheme to show a clear correlation with pathogenesis, structure and composition of calculi.

Morphological and textural data are very significant and recent classifications also deal with this kind of observations to distinguish eight types of urinary stones and at least 30 sub-categories (tab. 4).

On the contrary, previous categories were distinguished only on chemical bases (oxalate, phosphate, urate and cystine). This tends to underestimate the complexity of an individual's stone history as, indeed, it has been determined that the vast majority of stones actually contain more than one type of mineral.

The papers published in the past (Brien et al., 1982; Elliot, 1973; Herring, 1962; Murphy & Pyrah, 1962; Kim, 1982; Leusmann, 1991) must be considered the first step for making a fundamental tool in clinical uses. Finally, in 1993, Daudon et al. (1993) established the first classification of renal calculi with a clear correlation with the main urinary etiologic conditions. However, this information is complex and probably is difficult to adapt to clinical routine practice, in spite of its interest for scientific purposes. Consequently, it was necessary to establish a classification of renal calculi, in accordance to its composition and fine structure, clearly correlated with specific pathophysiological conditions as the main urinary alterations, adapted to the common clinical practice.

The latest classification scheme suggested (Grases et al., 1998, 2002) is very detailed and is useful for classifying each type of kidney stone, and, therefore, each patient in more than 30

different subgroups characterized by specific etiologic factors necessary to determine the treatment and disease prevention, especially in the presence of mixed stones requiring a proper intervention for each mineral phase present.

This classification constituted the first attempt to set up a classification of renal calculi useful for clinical purposes and also the first effort to find the relationships between pathogenesis, structure and composition of calculi, yet no connections with urinary parameters were established.

GROUP	Description	TYPE	Description	SUBTYPE	Description
1	Calcium oxalate monohydrate (whewellite) - papillary kidney stone	1a	core constituted by whewellite / organic matter	1aI	core constituted by organic matter
				1aII	core constituted by weddellite and organic matter
		1b	core constituted by hydroxyapatite/organic matter	1bI	core constituted by hydroxyapatite
				1bII	core constituted by hydroxyapatite and organic
2	Calcium oxalate monohydrate (whewellite) - kidney stone in cavity	2a	core constituted by whewellite + organic matter		
		2b	core constituted by hydroxyapatite + organic matter		
		2c	core constituted by uric acid		
3	Calcium oxalate dihydrate (weddellite)	3a	weddellite only	3aI	without transformation in whewellite
				3aII	with transformation in whewellite
		3b	hydroxyapatite in small quantities	3bI	core constituted by hydroxyapatite
				3bII	containing little amounts of hydroxyapatite among weddellite crystals
				3bIII	containing little amounts of hydroxyapatite and organic matter among weddellite crystals
3c	papillary				
4	Weddellite + Hydroxyapatite mixed stone			4I	alternative weddellite/hydroxyapatite layers
				4II	disordered weddellite/hydroxyapatite deposits
5	Hydroxyapatite	5a	hydroxyapatite only		
		5b	weddellite in small quantities		
6	Struvite				
7	Brushite				
8	Uric Acid	8a	uric acid only	8aI	compact uric stone
				8aII	layered uric stone
				8aIII	disordered uric stone
		8b	uric acid + uric acid dihydrate	8bI	alternative anhydrous/dihydrate uric acid layers
				8bII	disordered anhydrous/dihydrate uric acid deposits
8c	urates				
9	Whewellite + uric acid mixed stone			9I	papillary stone
				9II	unattached (no papillary) stone
10	Cystine				
11	Infrequent stones	11a	organic matter as main components		
		11b	medicamentous		
		11c	artefacts		

Table 4. Classification scheme

5. Stone analyses procedures

Because most stones are multicomponent, the method employed in the analysis of stone material should be capable of resolving all components of the stone, especially all the crystalline components.

The literature on stone analysis methods clearly supports the use of XRD or FTIR as the prime choices. One issue not yet resolved in the literature is the level of accuracy one should accept in analysis reports and the rank order of compositional analysis in multicomponent stones.

A possible example of a recommended procedure to analyse urinary stone is explain in the figure 11.

The mission of the laboratory is to provide information necessary for clinical decision making and patient care.

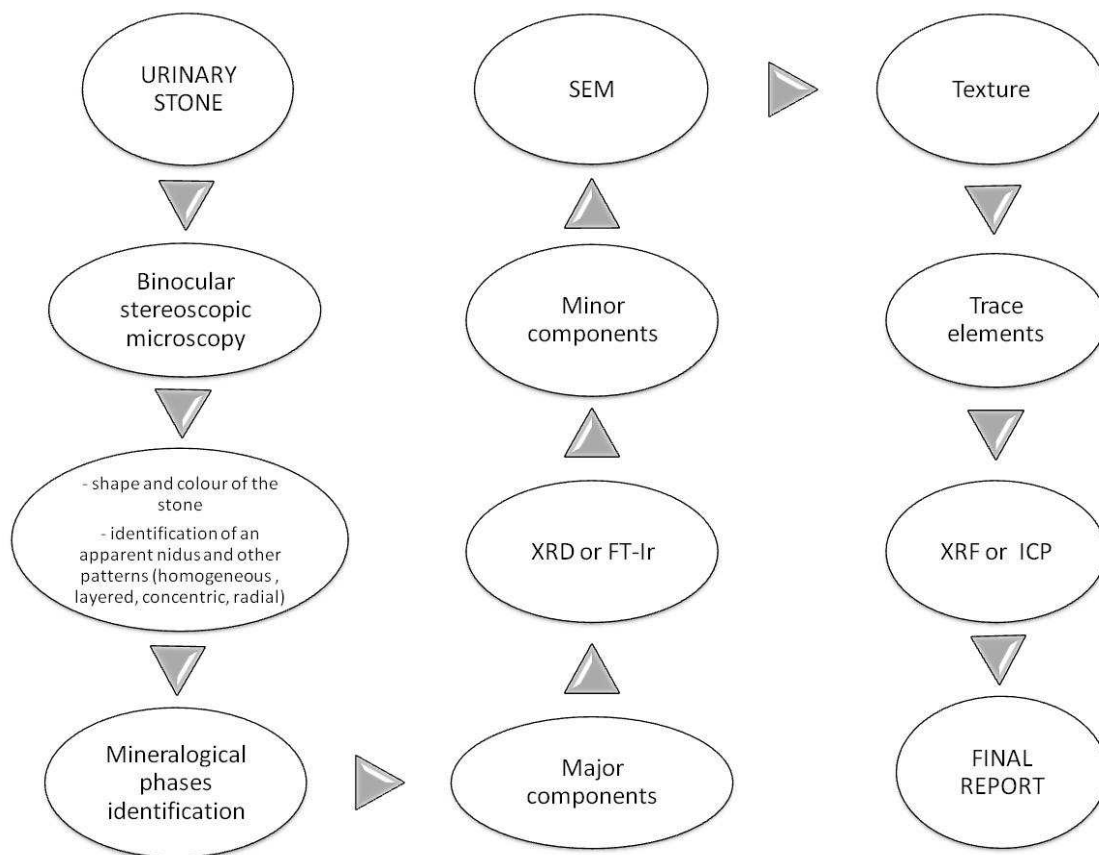


Fig. 11. Flow pattern of urinary stone analysis

Laboratory analyses generate multiple different data types that may include text, quantitative, graphic, and digital image data. Combining the different types of data produced during laboratory analyses into a comprehensive report can maximize the effectiveness of the information presented to clinicians who are relying on the report to guide diagnostic and therapeutic decisions.

Unfortunately, these data types often reside in multiple separate systems, and integrating them into a report often requires laborious procedures, which are inefficient and fraught with potential for error. The management of data produced during kidney stone analysis is an example of such a situation.

The KISS system developed by Shang-Che Lin et al. (2002) is a good example to integrate patient and specimen information from the laboratory information system, digital images of stones, and analytic instrument data into a concise report for the ordering clinicians. The database management environment facilitates archival and retrieval capabilities. Implementation of the system has reduced the number of manual steps necessary to produce a report and has saved approximately 30 technologist hours per week. Transcription errors have been virtually eliminated.

6. Conclusion

Table 5 shows a summary of the comparative assessment of the various methods of stone analysis. It may be inferred that any of these methods is only as good as the sample used, and different areas of the stone must be analyzed separately if useful results are to be obtained.

While the wet chemical analytical qualitative method of urinary stone remains the traditional gold standard, these have been increasingly globally replaced with the more accurate and quantitative methods, such as infrared spectroscopy and X-ray diffraction.

Unfortunately, many urologists make no use of stone analysis due to cost reasons, ignorance, or convenience.

	Chemical analysis	Thermal analysis	SEM	X-ray diffraction	Infrared spectroscopy	Polarization microscopy
Relative cost factor	****	***	*	**	**	****
Analysis Time	**	**	*	***	****	*
Sample preparation	**	**	*	***	***	****
Degree of accuracy	**	***	***	****	***	*

Table 5. Analysis of different methods of urinary stone analysis (****= good; *=bad)

7. References

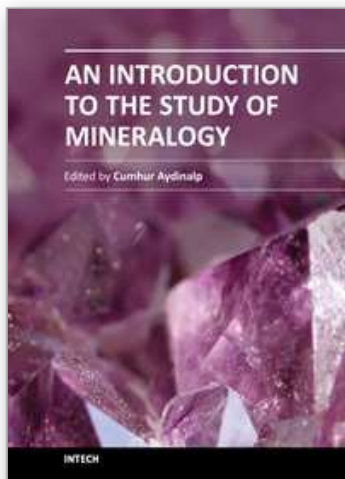
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