

What is the State of the Stone Analysis Techniques in Urolithiasis?

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Purpose: To compare and evaluate the mostly used methods of urinary stone analysis.

Materials and Methods: We searched PubMed and Google Scholar for “urolithiasis, nephrolithiasis, renal stone, and kidney stone” combined with “stone analysis, spectroscopy, X-ray diffraction, chemical analysis, mass spectrometry, and laser-induced breakdown spectroscopy, review article, and quality control assessment.”

Results: We identified 24 articles about reviews of the principles of stone analysis techniques and their quality control trials. Seven articles were not in English language; hence, were omitted from this review. The remaining 17 articles and their related references were studied thoroughly. There are various chemical and physical techniques available for urinary stone analysis. The correct stone analysis has to identify not only all stone components, but also the molecular structure and crystalline forms of them with the exact quantitative determination of each component.

Conclusion: The knowledge of urinary stone composition is important for understanding pathophysiology, choice of treatment modality, and prevention of recurrences of urolithiasis, but up to now, a standard method has not been defined. Although there are many techniques available for identifying the urinary stone composition and structure, no single method can provide all the requiring information. Therefore, a combination of structural and morphological tests is needed for this purpose.

Keywords: kidney calculi, chemical analysis, spectroscopy, X-ray diffraction

INTRODUCTION

The incidence of nephrolithiasis has considerably increased throughout the world in the last twenty years.^(1,2) The treatment of urinary stone can be painful, stone removal often requires surgery, and renal failure occurs in about 3% of patients.⁽³⁾ Furthermore, the recurrence rates may be as high as 10% to 23% per year and may reach 50% within 5 years if a proper management, stone analysis, and follow-up are not applied.⁽⁴⁾

The most frequent component of urinary calculi is calcium, which is the major constituent of nearly 75% of stones. Urinary stone is mostly composed of calcium oxalate about 60%, mixed calcium oxalate and hydroxy apatite 20%, uric acid approximately 10%, struvite (magnesium ammonium phosphate) about 10%, brushite 2%, and cystine 1%.⁽⁵⁾ The purposes of stone analysis are qualitative differentiation of all stone components and their semiquantitative determination.⁽⁶⁾ The aim of this review is to compare the principles and practical application of various chemical and physical techniques used for urinary stone analysis.

MATERIALS AND METHODS

According to our search on PubMed and Google Scholar for “urolithiasis, nephrolithiasis, renal stone, and kidney stone” combined with “stone analysis, spectroscopy, X-ray diffraction, chemical analysis, mass spectrometry, and laser-induced breakdown spectroscopy, review article, and quality control assessment.”

RESULTS

We identified 24 articles about reviews of the principles of stone analysis techniques and their quality control trials. Seven articles were not in English language; hence, were omitted from this review. The remaining 17 articles and their related references were studied thoroughly.

Currently, the following methods are available for stone analysis: Wet chemical analysis, ther-

mogravimetry, optic polarizing microscopy, scanning electron microscopy, and different methods of spectroscopy. At first, we describe the principles of these methods and then, compare their accuracy and practical application according to our literature review.

Wet Chemical Analysis

Although wet chemical technique is the most widely used approach for stone analysis in routine laboratories, it can only identify the presence of individual ions and radicals without differentiating a specific compound in many stone types and mixtures.⁽²⁾ An external quality assurance scheme showed relatively poor performance of qualitative and semi-quantitative wet chemical tests, including commercial kits.⁽⁷⁾ However, its performance can improve by using quantitative wet chemical approach, in which the same routine quantitative chemical analysis methods for blood and urine are used for a suitably prepared solution of the stone.⁽²⁾

Thermogravimetry

Since the 1970s, thermogravimetric analysis (TG or TGA) has been extensively applied for analyzing kidney stones.⁽⁸⁾ Thermogravimetry is a viable, fast, and simple technique based on continuous recording of both the temperature and weight loss of the material during a progressive temperature increase to 1000 °C in an oxygen atmosphere.

As each substance has its own specific type of transformation, the starting and ending temperature of transformation, the amount of change in weight, and enthalpy, the nature of the substance will be clarified by the pattern of weight change and the magnitude of this change indicates the proportion.⁽²⁾

Optic Polarizing Microscopy

The base of this technique is the interaction of polarized light with crystals of stones. After the stone is fractured and the material is removed from various points of it, it can be assessed under the polarizing microscope using a drop of the appropriate refractive index liquid.⁽⁹⁾ Parameters which iden-

tify the stone minerals include the color, refraction of light, and double refraction.⁽⁶⁾

Scanning Electron Microscopy (SEM)

Scanning electron microscopy is a precise technique for the study of morphology of urinary calculi. This technique is non-destructive and reveals details about stones 1 to 5 nm in size,⁽¹⁰⁾ without changing the specific morphology of the components.⁽²⁾ Furthermore, it can produce very high-resolution images of a sample surface.

Spectroscopy

Spectroscopy is the study of the interaction between matter and radiated energy. Spectroscopy techniques can be classified in several ways which are summarized in Table 1.^(11,12) Here the principles and practical application of mostly used methods of spectroscopy will be presented.

Infrared (IR) Spectroscopy

Infrared spectroscopy was used firstly in 1955;⁽¹³⁾

however, it has become as a popular reliable method for in-vitro quantitative stone analysis in the last decade.⁽¹⁴⁾ Infrared spectroscopy is a specific, rapid, and versatile method, which uses IR radiation in order to cause atomic vibrations, consequently, energy absorption and finally, appearance of absorption bands in the IR spectrum of stone samples.⁽²⁾ Two different IR spectroscopy approaches are common: The direct IR transmission, in which, the stone material is mixed with potassium bromide and compressed to form a disc, which is used for the analysis. Therefore, stone material cannot be recovered for further supporting analysis, such as wet chemical tests.⁽²⁾ But in non-destructive approach, such as photo-acoustic detection,⁽¹⁵⁾ recovery of the sample is possible.

A more recent technique in IR spectroscopy is the method of attenuated total reflection technique (ATR), which is applicable for soft samples.⁽⁶⁾ Fur-

Table 1. Classification of the spectroscopy techniques.

1. Type of radiated energy	
Electromagnetic radiation	Classified by the wavelength region of the spectrum and includes microwave, terahertz, infrared, near infrared, visible and ultraviolet, x-ray, and gamma spectroscopy.
Particles	Electrons and neutrons can also be a source of radiative energy
Acoustic spectroscopy	Involves radiated pressure waves
2. Nature of the interaction	
Absorption	
Emission	
Elastic scattering and Reflection spectroscopy	Determines how incident radiation is reflected or scattered by a material, such as X-ray Diffraction
Impedance spectroscopy	
Inelastic scattering	Raman scattering
Coherent or resonance spectroscopy	Nuclear magnetic resonance (NMR) spectroscopy
3. Type of material	
Atoms	Atomic absorption spectroscopy (AAS) Atomic emission spectroscopy (AES) Flame emission spectroscopy Inductively coupled plasma atomic emission spectroscopy X-ray spectroscopy X-ray fluorescence (XRF)
Molecules	Infrared and Raman spectroscopy
Crystals	
Nuclei	NMR spectroscopy

thermore, sample preparation for this technique is very easy, as it does not require mixing the sample with an IR inactive material, such as potassium bromide, prior to analysis.

X-Ray Powder Diffraction (XRD)

X-ray powder diffraction uses monochromatic X-rays for identifying the constituents of a renal stone based on the unique diffraction patterns produced by a crystalline material. Crystal moieties of a structure diffract or reflect the penetrated X-rays in particular patterns.⁽²⁾

Elementary Distribution Analysis (EDAX)

Elementary distribution analysis (EDAX) is used to obtain the percentage of composition of all stone sample elements and is significantly useful for recognizing unknown crystals not identified by ordinary light microscopy or SEM alone. Elementary distribution analysis can be used to confirm the SEM results and also evaluate the percentage of the different elements present in a sample.⁽¹⁶⁾

DISCUSSION

Nephrolithiasis is a recurrent condition with considerable morbidity. While in symptomatic stone episodes the appropriate treatment is necessary, prophylactic workup to prevent recurrences is also of great importance, which is possible by a complete metabolic workup and a suitable stone analysis.⁽¹⁴⁾

The chemical composition of urinary calculi was firstly reported at the end of the 18th century, when important chemical components of urinary calculi, such as uric acid (Scheele 1776) and cystine (Wollaston 1810) were discovered. After the systematic studies by Heller (1847) and Ullmann (1882), the chemical analysis of urinary calculi was presented as an established routine.⁽¹⁷⁾

In 1947, Prien and Frondel introduced the polarizing microscopy as an analytical tool for identification of the crystalline constituents of calculi by refractive index measurements.⁽¹⁸⁾ The ability to identify specific minerals, the capability to ana-

lyze small amounts of stones, and the rapidity of polarizing microscopy are the advantages of this technique over chemical analysis. Silva and colleagues studied a sample of 50 stones retrieved from patients in Brazil in order to compare the chemical with morphological kidney stone composition analysis. They found that unlike morphological analysis, chemical analysis can only detect calcium and oxalate separately without differentiating the crystalline types. Identifying the crystalline form is very useful for planning therapy, eg, calcium oxalate dehydrate (COD) is associated with hypercalciuria while calcium oxalate monohydrate (COM) is more closely related to hyperoxaluria. Therefore, they offered using both types of analysis routinely for a better understanding of the mechanisms involved in lithogenesis.⁽¹⁹⁾

Jhaumeer-Laulloo and Subratty employed wet chemical tests and IR spectroscopy techniques to analyze kidney stones from 12 patients. Their findings revealed that the chemical analysis method was not accurate and could result in significant clinical errors. They also showed that the spectroscopic methods were applicable for smaller amount of sample and were able to identify the different constituents of the renal stones.⁽²⁰⁾

Singh analyzed urinary stones of 50 patients by Fourier Transform IR (FT-IR) and offered that FT-IR is an efficient and accurate technique to determine urinary stone composition. He also mentioned that using computerized IR spectrophotometer and large reference library enable us to determine exact quantitative stone composition, and this method should be extended to all urolithiasis centers.⁽¹⁴⁾

While Estepa and coworkers depicted the possibility of false identification during using IR because of library incompleteness and also considerable differences between the spectra of natural and synthetic compounds. For example, they observed that the spectrum of human whewellite shows a peak at 1315 cm⁻¹ while the peak is at 1319 cm⁻¹ for the synthetic one. On the other hand, a peak at

1319 cm^{-1} in human stone samples corresponds to a mixture of whewellite and weddellite in 50/50 proportions.⁽²¹⁾ Therefore, false identification of weddellite may occur using the search procedure if synthetic whewellite is included as a reference in libraries.

Rose and Woodfine used TGA for the analysis of stones and supported its ability to produce fast and quantitative results.⁽²²⁾ However, limitations of TGA require relatively large amount of material for optimal resolution and non-recovery of sample. Furthermore, similarity in ignition temperatures and rates of disintegration of some closely related compounds, such as purines, may make the identification difficult. As calcium phosphate (apart from the brushite form: $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$), silica, and calcium pyrophosphate display very little weight change on heating, TGA cannot convincingly identify them from each other.⁽²⁾

Since 1970s, physico-chemical techniques have been increasingly employed for urinary stone analysis, which resulted in discovering numerous crystalline elements in urinary stones.⁽²³⁾ Many clinical laboratories employed X-ray diffraction and IR spectroscopy as reference techniques for stone analysis. Thereafter, a lot of studies were designed to compare the quality of these methods^(24,25) in addition to quality control surveys that were conducted for improving the standards of them,⁽²⁶⁾ some of which are presented as follows.

Rebentisch presented the result of six external quality assessment surveys of averagely 40 laboratories from 23 countries that used six quantitative and various qualitative analytical techniques during 1983 and 1988. He used both standard of quality and the mean deviation as two determining parameters for ranking the methods, which were from the best performance to worst in the following order: X-ray diffraction, IR spectroscopy, ultramicrochemical analysis (UMCA), polarization microscopy (MI), differential thermoanalysis (TA) and quantitative chemical analysis (QTCA).⁽²⁷⁾ Ac-

ording to these results, Rebentisch offered that X-ray diffraction and IR spectroscopy methods give comparable and highly acceptable analytical results and can be classified as reference methods for the analysis of urinary calculi.⁽²⁷⁾ The fourth International Ring Test for checking the quality of methods for urinary calculus analysis, conducted by Rebentisch and colleagues in 1988, demonstrated that the method of XRD is clearly superior to IR spectroscopy.⁽²⁸⁾ Also in external quality assessment of analysis of urinary calculi, which was commenced in 1991, they suggested that the use of chemical methods should be discontinued because of its unacceptable quality in approximately 40% of laboratories.⁽²⁹⁾

Hesse and associates designed a twice-yearly ring trials quality control survey to examine the quality of urinary stone analysis based on synthetic products in averagely 100 laboratories since 1980. The methods employed for these analyses were based on chemical analysis, IR spectroscopy, and X-ray diffraction. The results of 44 ring trials (1980 to 2001) illustrated that at first, the analyses were carried out using chemical methods for more than 80% of the participants. This figure considerably decreased to 13% in 2001. On the contrary, the use of IR spectroscopy progressively increased to 79%. The number of specialized laboratories which used X-Ray diffraction was constantly about 5% to 9%. Additionally, these ring trials revealed that error rates for IR spectroscopy and X-ray diffraction were only limited to individual substances, whereas for the chemical methods very high proportion of errors occurred with both the pure substances and binary mixtures (6.5% to 94%). Therefore, the majority of laboratories stopped using chemical analysis, which is now considered to be obsolete.⁽²⁶⁾

Kasidas and associates analyzed the results of external quality assurance for urinary stone analysis in Great Britain during 1992 and 2001. According to their findings, most of the participating labora-

tories (80%) used wet chemical analysis with only 55% to 65% accuracy versus IR with 85% to 90% correct analyses.⁽²⁾ Another study in china confirmed the reliability and accuracy of X-ray diffraction for qualitative and quantitative analysis of urinary stones.⁽³⁰⁾

The benefits and disadvantages of the most common techniques based on the reviewed studies are summarized in Table 2.^(2,6,14,31)

In addition to the most common techniques that were mentioned above, there are other techniques which may have in-vivo application in practice or reveal more detailed information on fine molecular structure or several unexpected trace elements mainly in the nuclear region of the stones. Meanwhile, often these techniques are not useful in routine laboratory for being costly and requiring special expertise or sample preparation.

Kim and colleagues analyzed 86 consecutive urinary stones by X-ray analysis and compared the findings with those of three other methods: X-ray diffraction, IR spectrometry, and chemical analysis. This study indicated that the sensitivity of X-ray analysis was several times more than other three methods, especially in detection of apatite. This study also offered X-ray analysis as a particularly suitable method for detection of rare inorganic components of urinary stones, such as silica and gypsum.⁽³²⁾

Batchelar and coworkers revealed that the X-ray coherent scatter analysis is a novel technique for intact stone analysis using monoenergetic X-ray from the standard diagnostic X-ray equipment.⁽³³⁾

Because the coherent scatter properties is related to the molecular structure of the scattering media of each of the stone components, COM, cystine, magnesium ammonium phosphate, and calcium phosphate showed a distinct coherent scatter pattern, which matches that of a pure chemical sample. Wignall and associates suggested that coherent X-ray scatter would be useful in future studies of the ability of commercial laboratories because it can

visualize even small struvite regions in stones.⁽³⁴⁾ Siritapetawee and Pattanasiriwisawa used X-ray absorption near-edge spectroscopy (XANES) and XRPD for analyzing 15 human urinary stones. Comparing the result of XANES spectra of unknown compounds from human kidney stones with the diffractogram data of the XRPD, it was shown that these two techniques agreed well with each other, while XANES required a smaller amount of each sample than XRPD for analysis.⁽³⁵⁾

In 1995, the use of nonenhanced computed tomography (CT) imaging to identify urolithiasis was first reported by Smith and associates and now it has become the standard diagnostic tool for evaluation of patients with renal colic.⁽³⁶⁾ Due to the emergence of noncontrast CT (NCCT) in the assessment of acute flank pain and the subsequent availability of the attenuation coefficient measurement, several groups were interested in comparing attenuation and stone composition in vitro. Studies involving the use of single-energy CT technology have shown that some information about stone composition may be gained, enabling differentiation between uric acid and calcium stones on the basis of their different attenuations, with lower attenuation values (in Hounsfield units) for uric acid stones.⁽³⁷⁾ The difficulty in these studies was related to the considerable overlap of attenuation values, which prevented high levels of specificity.⁽³⁸⁻⁴⁰⁾

Dual-energy CT by low and high-energy scanning is capable to differentiate various materials with similar electron densities, but different photon absorption.⁽³⁷⁾ Therefore, it may not only contribute to the identification, but also to the chemical characterization of stones in the urinary tract, which could be useful in surgical or medical treatment decisions. Hidas and coworkers used dual-energy CT to pre-operatively assess the composition of urinary stones in 27 patients and compared the results with postoperative in-vitro X-ray diffraction analysis. They found that dual-energy CT was able to characterize the kidney stone composition with

82% accuracy. But this technique could not identify struvite stones which had attenuation ratios that overlapped with calcified stone ratios, and thus could not be assessed reliably.⁽³⁷⁾

By combination of X-ray attenuation values and morphological appearance, micro CT can identify fine stone structure and its mineral component,⁽⁴¹⁻⁴³⁾ especially for apatite.^(41,44,45) Furthermore, detection of the following 6 minerals, uric acid, COM, COD, cystine, struvite, and hydroxy apatite, in pure or heterogeneous urinary stones is possible without having overlapped ranges of micro attenuation values.^(46,47) However, the study by Krambeck and associates revealed that the identification of minerals with lower X-ray attenuation, such as struvite, is not always possible as a minor inclusion in particular mineral. In addition, its use in routine laboratory has not been exploited because it costs 10 times more than FT-IR.⁽⁴⁸⁾

Laser-induced breakdown spectroscopy (LIBS) is a simple, rapid, and remote technique, which permits real-time qualitative and quantitative identification of the major and trace elements present in the calculus.⁽⁴⁹⁾ In this technique, a pulsed laser beam is focused on the surface of the sample in order to produce high-density plasma that excites various atomic elements and elemental transitions in the focal volume. Singh and associates performed LIBS to estimate the quantitative elemental constituents distributed in different parts of the kidney stones obtained directly from 5 patients by surgery, and compared the results with that of inductively coupled plasma mass spectrometry (ICP-MS). Both LIBS spectra and ICP-MS analysis showed that the major constituent of the kidney stones was calcium.⁽⁴⁹⁾

Laser ablation inductively coupled plasma mass spectrometry (LA ICP-MS) is a novel technique for the study of biological and geological samples,⁽⁵⁰⁾ which uses a focused laser beam issued to mobilize sample material as droplets or vapor from the sample surface. Thereafter, the material is

transported to the plasma often by argon as a carrier gas. The plasma causes the material to be ionized and moved through to the mass spectrometer, which selectively detects ions at a given mass-to-charge ratio.⁽⁵¹⁾

Kontoyannis and colleagues analyzed mineral components of a urinary stone forming layers with the use of three spectroscopic methods: Raman spectroscopy (RS), FT-IR, and XRD. Raman spectroscopy could analyze the various mineral layers in the kidney stones by focusing the laser beam at the desired layer, whereas application of FT-IR produced overlapping broad bands and XRD could not analyze the mineral components of the various layers of small stones precisely since the material contained in these stones was not sufficient.⁽⁵²⁾

In the study by Cytron and associates, analysis of chemical composition of the stones and their concentrations were determined by analysis of the urine samples from 24 patients based on fiberoptic IR spectroscopy. The urine samples were collected within 4 hours after extracorporeal shockwave lithotripsy. This study offered that fiberoptic IR can be applied as an alternative method for complete and quick metabolic evaluation of patients without sample preparation.⁽⁵³⁾

According to the studies described above, there are many different methods available for urinary stone analysis, but the fact is that no single method is sufficient to provide all the clinically useful information about the structure and composition of the stones. Therefore, a combination of these techniques is advised. Fazil Marickar and coworkers revealed that the combination of optical microscopy and IR spectroscopy of core, cross section, and surface of calculi is an accurate and reliable method for identification of the stone structure, its crystalline composition, and quantification of stone components while being highly cost-effective.⁽⁵⁴⁾ Uldall showed that combination of X-ray diffraction or IR spectrometry and wet chemistry may be suitable as reference methodology.⁽⁵⁵⁾

In the literature, other combinations of methods, such as TGA with X-ray diffraction by Konjiki and colleagues,⁽⁵⁶⁾ and TG with FT-IR spectroscopy by Materazzi and associates,⁽⁵⁷⁾ have been mentioned. Also, Fazil Marickar and coworkers analyzed 10 mixed stones using FT-IR spectroscopy and SEM-EDAX combination in order to get a thorough understanding of mixed stone morphology, and concluded that although FT-IR analysis is more modern, less time-consuming, and more precise, combination of SEM-EDAX will give a clear indication of the structure of the stone on the surface and interior in addition to exact quantification of all stone elements.⁽³¹⁾ More importantly, the study by Schubert revealed that useful results of any of these methods are obtained when different areas of

the calculus are analyzed separately.⁽⁶⁾

CONCLUSION

In this review, we observed that although wet chemical analysis technique of urinary stone is the traditional gold standard, it has been replaced with more accurate spectroscopy techniques, such as FT-IR, XRD, CT scan, etc. Also we believe that our current results provide compelling evidence to support the notion that in addition to applying combination techniques, analysis of different parts of stone separately is of utmost importance.

CONFLICT OF INTEREST

None declared.

Table 2. Comparison of the stone analysis techniques.

Test	Advantages	Disadvantages
Chemical analysis	<ul style="list-style-type: none"> • Easy • low cost 	<ul style="list-style-type: none"> • Time-consuming • Requiring large stone samples; hence, unsuitable for tiny stones • Only identification of the presence of individual ions and radicals rather than a specific compound, eg, unable to distinguish between the two commonly occurring calcium stones (monohydrate/dihydrate)
Polarization microscopy	<ul style="list-style-type: none"> • Cost-efficient • Quick examinations • Possibility to analyze very small samples • Ability to detect very small contents of components in the stone* 	<ul style="list-style-type: none"> • High subjective experience is necessary • Differentiation of components is difficult in some cases in the groups of uric acid, purine derivatives, and calcium phosphates
Infrared spectroscopy	<ul style="list-style-type: none"> • Moderate cost • Quick examination • Possibility to examine small samples • Easy preparation when using Attenuated Total Reflection technique • Semiautomatic evaluations are possible applying search-match functions • Useful for identification of organic components or noncrystalline substances, eg, purines, proteins, or fat and drug metabolites 	<ul style="list-style-type: none"> • Time-consuming pre-analytic preparation • The proper homogenization of the sample with potassium bromide may affect the Infrared spectroscopy spectrum quality • Resolution of the apparatus and reproducibility of the spectrum bands may affect its reliability • Difficulty in detection of small amounts of components in some cases, eg, whewellite in weddellite or reverse, or urates and uric acid dihydrate in uric acid • Difficulty in detection of some components due to overlapping of their absorption band, such as carbonate in struvite stones or cystine in whewellite or uric acid stone
X-ray diffraction	<ul style="list-style-type: none"> • Easy preparation • Automatic measurement • Quantitative analysis • Exact differentiation of all crystalline components is possible 	<ul style="list-style-type: none"> • High cost • Unable to detect noncrystalline or amorphous substances
Thermogravimetry	<ul style="list-style-type: none"> • Fast • Simple 	<ul style="list-style-type: none"> • Requiring relatively large amount of sample • Non-recovery of sample • Difficulty in identifying closely related compounds, eg, purines
Scanning electron microscopy	<ul style="list-style-type: none"> • Non-destructive • Possibility to visualize the components without altering their spatial orientation and specific morphology 	<ul style="list-style-type: none"> • High cost

* Whereas Kasidas and colleagues in another study showed that the Polarization microscopy cannot identify small amounts of crystalline material in mixtures.⁽²⁾

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