Analysis of stones formed in the human gall bladder and kidney using advanced spectroscopic techniques

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Abstract

Stone diseases (gallstones and kidney stones) are extremely painful and often cause death. The prime aim of biomedical research in this area has been determination of factors resulting in stone formation inside the gallbladder and urinary tract. Many theories have been put forward to explain the mechanism of stone formation and their growth; however, their complete cycle of pathogenesis is still under debate. Several factors are responsible for stone formation; however, much emphasis is placed on the determination of elemental and molecular composition of the stones. In the present review article, we describe different kinds of spectroscopic techniques such as Fourier transform infrared spectroscopy (FTIR), X-ray fluorescence (XRF) spectroscopy, time-of-flight secondary ion mass spectrometry (TOF-SIMS), and laser-induced breakdown spectroscopy (LIBS) and highlight their use in the analysis of stone diseases. We have summarized work done on gallstones and kidney stones using these advanced techniques particularly over the last 10 years. We have also briefly elaborated the basics of stone formations inside the human body and their complications for a better understanding of the subject.

Keywords Gallstones · Kidney stones · FTIR · WDXRF · EDXRF · TOF-SIMS · And LIBS

Stone formation inside humans and their complications

Stone formation inside the gallbladder and kidney are serious and painful diseases which affect a significant percentage of the population worldwide (Harding Rains 1964; Rao et al. 2011; Ramaswamy et al. 2015; Afdhal 2004; Berhoft et al. 1984; Trotman et al. 1974). Many theories have been put forward to explain the mechanism of stone formation and their growth; however, their pathogenesis is still under debate. Over the last few years, the prime aim of stone-based biomedical research has been the measurement of the atomic and molecular composition of the stone and correlation of this information to patient abnormalities (Rao et al. 2011; Ramaswamy et al. 2015). In this regard trace elements play an important role in many biological activities. Excess and deficit levels of

heavy and trace elements can induce pathological states. Stone formation inside the body can cause serious problems if untreated. Gallstones can damage the digestive system, and kidney stones can similarly injure the kidneys and urinary tract. In the following sections, we present a brief discussion on the types of gallstones and kidney stones and complications arising from their presence inside the human body.

Gallstones

Gallstones (pebble-like substances that develop inside the human gallbladder) are one of the most painful biliary tract diseases in adults with a particularly high incidence in India (Harding Rains et al., 1964; Singh et al. 2008; Cox et al. 2018). Gallstones form when bile stored in the gallbladder hardens into pieces of stone-like material. Bile is a bitter yellow or green fluid secreted by liver hepatocytes of most vertebrates and then stored in the gallbladder and used in the digestion of fats (Harding Rains 1964; Afdhal 2004; Cox et al. 2018; Di Ciaula et al. 2018; Reshetnyak 2012). Upon contraction, the gallbladder pushes bile into the common bile duct which then carries it to the small intestine, where it carries out its fat digestion role. The composition of bile includes water, cholesterol, fats, bile salts, proteins, and bilirubin

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(Harding Rains 1964; Rao et al. 2011; Ramaswamy et al. 2015; Afdhal 2004; Berhoft et al. 1984; Trotman et al. 1974; Reshetnyak 2012). Generally, bile is able to dissolve cholesterol (Fig. 1a) but if there is too much cholesterol then it will form into crystals that eventually grow into stones. In certain conditions, if the level of bilirubin (Fig. 1b) is too high then this will also contribute to stone formation.

Different kinds of gallstones have their own causes and formation mechanisms. The composition of gallstones is affected by such factors as age, diet, geographical region, obesity, weight loss, and ethnicity among others (Harding Rains et al., 1964; Afdhal 2004; Di Ciaula et al. 2018; Reshetnyak 2012). It is difficult to define an ideal gallstone classification system; however, they can be broadly grouped based on their major chemical compositions. On this basis, they can be divided into the following three main types: (i) cholesterol stones, (ii) pigment stones, and (iii) mixed stones.

- i). Cholesterol gallstones: These are the most common type of gallstones made primarily of cholesterol. Cholesterol (a white crystalline powder) is one of the substances secreted by the liver cells into bile. In this process, the liver eliminates excess cholesterol from the body. The chemical formula of the cholesterol is $C_{27}H_{46}O$ and its chemical structure is shown in Fig. 1a. Fatty cholesterol is dissolved in bile so that it can be carried through the ducts. If the liver secretes too much cholesterol (greater than the amount of bile acids and lecithin), some of the cholesterol remains undissolved. Similarly, if the liver does not secrete enough bile acids and lecithin, some of the cholesterol also does not dissolve. Thus in both cases, the undissolved cholesterol sticks together and forms particles of cholesterol that grow in size and eventually form larger gallstones (Harding Rains et al., 1964; Afdhal 2004; Reshetnyak et al. 2018).
- ii). Pigment gallstones: These kinds of stones are defined as any brown to black stones and composed of calcium salts of bilirubin (such as calcium bilirubinate),

phosphate, carbonate, and other types of anions. Pigment is a waste product formed from hemoglobin (Singh et al. 2008; Reshetnyak et al. 2018). Hemoglobin is a protein that carries oxygen throughout the body in red blood cells (RBCs). The hemoglobin from old RBCs targeted for destruction is changed into bilirubin and released into the blood. Bilirubin is removed from the blood by the liver (Singh et al. 2008; Afdhal 2004; Reshetnyak et al. 2018). The liver modifies the bilirubin and secretes the modified bilirubin into bile. The chemical formula of bilirubin is $C_{33}H_{36}N_4O_6$ and its chemical structure is shown in Fig. 1b. If there is too much bilirubin in bile, the bilirubin combines with other chemical constituents within bile to form pigments of brown color. Pigment dissolves poorly in bile and sticks together to form particles that grow in size and eventually form hard pigment type gallstones of black and brown color. The pigment gallstones that form in this manner are called black pigment gallstones and their color ranges from brown to black and they are physically hard in character. Brown pigment gallstones are much softer than black pigment gallstones (Swobodnik et al. 1990; Cox et al. 2018; Afdhal 2004).

- iii). Mixed gallstones: These types of stones are a mixture of cholesterol and pigment stones consisting of varying proportions of cholesterol and bilirubinate salts. They are also composed of other components such as calcium carbonate, calcium phosphate, bilirubin, calcium bilirubinate, calcium palmitate, and calcium stearate (Singh et al. 2008). Due to their calcium content, they are often radiographically visible (Rao et al. 2011; Singh et al. 2008; Swobodnik et al. 1990; Afdhal 2004).

Gallstones are hard chemical particles that form and develop inside the gallbladder after a complex series of

Fig. 1 (a) Chemical structure of cholesterol and (b) bilirubin

events involving bile supersaturation, nucleation and initiation, and stone enlargement by accretion. Formation of gallstones is initiated by biliary stasis, infection, and/or mucin and their size increases nearly 3 mm per year quickly reaching up to a few centimeters in diameter. Gallstones occur in nearly 95% of patients with cholecystitis (Swobodnik et al. 1990; Cox et al. 2018; Reshetnyak et al. 2018). The chemical constituents of gallstones are complex and vary in a stone-to-stone manner depending upon the dietary habits of patients, their geographical region along with many more factors (Kleiner et al. 2002; Liu et al. 2002; Singh et al. 2009a; Malet et al. 1988; Wosiewicz 1983; Tabata and Nakayama 1981). Some rare types of gallstones have been also reported (Suzuki et al. 1975; Maki 1966).

As mentioned there are several factors which affect the formation of gallstones. Obesity is an independent factor leading to an increased incidence of gallstones in adults (Swobodnik et al. 1990; Cox et al. 2018; Afdhal 2004). The increased exposure to female sex hormones is also one of the factors that stimulate cholesterol excretion by the liver (Swobodnik et al. 1990; Cox et al. 2018; Afdhal 2004). The most important factor is the consumption of a “western diet” which results in cholesterol super-saturation within bile, favoring its precipitation and crystal growth (Di Ciaula et al. 2018; Cox et al. 2018). In Fig. 2, we have presented the different kinds of causes for the pathogenesis of cholesterol, mixed and pigment gallstones, and factors affecting their formation and growth.

Complications of gallstone disease

Gallstones can block the normal flow of bile if they move from the gallbladder and lodge in any of the ducts that carry bile from the liver to the small intestine. The ducts include the (i) hepatic ducts, (ii) cystic duct, and (iii) common bile duct (Swobodnik et al. 1990; Afdhal 2004). Hepatic ducts carry bile out of the liver, the cystic duct takes bile to and from the gallbladder, and the common bile duct takes bile from the cystic and hepatic ducts to the small intestine (Swobodnik et al. 1990; Afdhal 2004). Bile trapped in these ducts can cause inflammation in the gallbladder, the ducts, and in the liver. Other ducts open into the common bile duct, including the pancreatic duct, which carries digestive enzymes out of the pancreas. Most of the time, gallstones which pass through the common bile duct provoke inflammation in the pancreas (Swobodnik et al. 1990; Cox et al. 2018; Afdhal 2004). This condition is called gallstone pancreatitis, which is a very painful and critically dangerous. If any of the bile ducts remain blocked for a long period of time, severe damage can occur inside the gallbladder, liver, and pancreas. There are some warning signs of this serious problem such as fever, jaundice, and unrelieved pain. If left untreated, the condition can lead to death (Swobodnik et al. 1990; Cox et al. 2018; Afdhal 2004).

Presently, no effective drugs or medicine are available to treat gallstone diseases. Surgical removal of gallstones and also the gallbladder is the only solution to cure gallstone diseases. The most common complication in gallbladder surgery

Fig. 2 Pathogenesis of cholesterol, mixed and pigment gallstones and factors affecting their formation and growth

is injury to the bile ducts. An injured common bile duct can leak bile and cause painful and potentially dangerous infection. More detailed investigations on gallstones may provide sufficient information to disrupt this pathogenesis and possibly help in the development of a preventive treatment. More information may also help to develop safer methods of destroying stones, without the need for surgical treatment.

Despite many years of research, a complete explanation of gallstone formation is not available. It has been established that the principal chemical constituents of gallstones are cholesterol and calcium bilirubinate with other compounds including carbonate, phosphate, derivatives of cholic acid, fatty salts, proteins, and polysaccharide also being present (Kleiner et al. 2002; Liu et al. 2002; Singh et al. 2008). Significant variation in chemical composition of different gallstones occurs throughout the various regions of India (Rathnaswami 1998; Sarin et al. 1986; Singh et al. 2008). Cholesterol-type stones are more prevalent in the northern, eastern, and western regions (Singh et al. 2008; Rathnaswami 1998; Sarin et al. 1986). It has been reported that the seriousness of gallstone disease can be correlated with stone's constituents (Singh et al. 2008; Singh et al. 2009b; Liu et al. 2002). Thus, characterizing the stone composition is crucial both for research purposes and to enhance patient care.

Kidney stones

Stone formation inside the kidneys of the human body is a very painful nephrological disorder that is prevalent worldwide. It is also known as renal calculi and more broadly as urinary stones. Kidney stones are solid concretions (crystal aggregations) of dissolved minerals in urine (Collins 2005; Weaver et al. 2002). Kidney stones can vary in size from a few mm to a few centimeters. They typically leave the body by passage through the urine stream, and many stones are formed and passed without causing symptoms (Rao et al. 2011). Stones having a size more than 3 mm in diameter before passage can cause obstruction of the ureter. Such obstruction results in dilation or stretching of the upper ureter and renal pelvis as well as spasm of the associated muscle. Trying to pass, the stone can cause severe episodic pain, most commonly felt in the flank and lower abdomen (Rao et al. 2011).

Kidney stone type varies worldwide on the basis of geography and genetic predisposition (Rao et al. 2011). The occurrence of nephrolithiasis and its prevalence is on the rise across the world (Rao et al. 2011). It is strongly dependent upon such factors as the sex, obesity level, and age of the affected person (Romero et al. 2010). Kidney stone pathogenesis and the factors responsible for disease etiology is still not fully understood. Dietary intake may be among the various other factors associated with stone formation in addition to factors like hygiene, the quality of drinking water, and inherent metabolic disorder of the patient (Rao et al. 2011). Illness caused by

formation of stone(s) is accompanied by severe abdominal pain because of the mechanical irritation to the tissues of the urinary tract caused by movement of the stones. Very often, the size and surface roughness of the stone directly reflects in the severity of pain caused to the patient, and the exact details vary from patient to patient. A study of ureteral stone passage (Miller and Kane 1999) shows that in patients with ureteral stones less than 10 mm the passage of stone is spontaneous (with or without medical therapy), whereas in most of the cases when stone size is greater than 10 mm, the patient is required to undergo surgery for removal of the stones followed by subsequent preventive treatment to prevent its recurrence. The likelihood of recurrence is about 50% (Kim et al. 1985), and the selection of preventive measures depends upon the stone's chemical composition (Finkelstein and Goldfarb 2006).

Urinary stones exhibit varying chemical compositions and are quite specific to individual patients. A variety of organic and inorganic substances participate in stone formation. A majority of kidney stones can be classified into five categories (as can be seen from Fig. 3) based on their composition: calcium oxalate (70%), calcium phosphate (5 to 10%), uric acid (10%), struvite (15 to 20%), and cystine (1%) (Menon and Resnick 2002; Pietrow and Karellas 2006; Singh and Rai 2014). The details of the categorization of stones into calcareous stones and noncalcareous stones and their properties are described well by Singh and Rai (2014). Many stones have a mixed composition, with one type of crystal becoming a nidus for heterogeneous crystallization.

- i). Calcium containing stones: Most kidney stones contain calcium combined with oxalate, phosphate, or occasionally uric acid in the form of calcium oxalate, calcium phosphate, calcium carbonate, brushite, gypsum, and dolomite (Singh and Rai 2014). Calcium oxalate is a calcium salt of dicarboxylic acid and oxalic acid. Calcium oxalate crystallizes in two different chemical and crystallographic forms, i.e., calcium oxalate monohydrate and calcium oxalate dehydrate. These are also known as whewellite ($\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$) and weddellite ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$), respectively. These kinds of stones have been found to be opaque to X-rays or similar kind of radiations. (Singh and Rai 2014).
- ii). Uric acid stones: Uric acid stones are a crystallized mixture of uric acid and magnesium ammonium phosphate (struvite). These kinds of stones have been experimentally found to be radiolucent (Singh and Rai 2014). These types of kidney stones are very common in patients due to the precipitation of adenine, xanthine, and uric acid under low urinary pH condition.

Fig. 3 Classification of kidney stones based on their chemical composition

- iii). Struvite stone (triple phosphate stones): Struvite is a crystalline substance composed of magnesium ammonium phosphate (Singh and Rai 2014). These kinds of stones are formed due to infection and are thus referred as infection stones. Struvite stones typically present as large, gnarled, and laminated (as shown by radiography). The cross-section of struvite stones normally exhibit layers of white and brownish color (Singh and Rai 2014). Struvite stones are formed at high concentrations of ammonium and trivalent phosphate in alkaline urine containing urease produced by bacteria. These types of stones are more commonly found in women than in men (Rao et al. 2011).
- iv). Cystine stones: Cystine stones are formed due to the leakage of cystine into the urine. These kinds of stones get stuck inside the walls of either the kidneys or inside the urinary tract and can cause significant problems. Patients with cystinuria have been found to have an increased probability of stone recurrence and hence care and monitoring must be undertaken. Pure L-cystine stones are composed of very small yellow spheroids having a relatively homogeneous appearance (Singh and Rai 2014).
- v). Protease-related stones: These stones are found in HIV-positive patients and are associated with the use of indinavir sulfate which is a protease inhibitor used in anti-HIV treatment (Singh and Rai 2014). These stones are also not visualized on spiral CT scanning (Singh and Rai 2014; Rao et al. 2011).

As kidney stones are predominantly composed of calcium oxalate, in the present review article, our aim is to include the major aspects that cause calcium oxalate to precipitate. Figure 4 describes some of the factors influencing the etiology of kidney stone formation and presents the general steps involved.

Complications of kidney stones

Common complications from kidney stones are extreme pain which occurs suddenly when stones move in the urinary tract and blocks the flow of urine. This may lead to infection and

damage to the kidney. X-rays will detect a blockage, and large stones can be removed by surgical treatment. Surgery is not usually necessary, and most of kidney stones pass through the urinary system when the patients drink a significant volume of water. In cases involving large stones surgical treatment is required. Extracorporeal shock wave lithotripsy (ESWL) is the most frequently used procedure for the treatment of kidney stones (Rao et al. 2011). In ESWL, shock waves, created outside the body, travel through the skin and body tissues until they hit the denser stones. The stones break down into small particles which are more easily passed through the urinary tract in the urine. Several complications may occur with ESWL treatment. Patients may suffer from the flow of blood through their urine after treatment. Bruising and minor discomfort in the back or abdomen from the shock waves may also occur (Rao et al. 2011). In view of above complications and to prevent kidney stone formation and also to know the metabolic activity causing stone formation, it is essential to estimate the composition of stones.

A combined clinical and surgical approach is required to treat and manage kidney stones. Substantial progress has been made in the investigation of kidney stone formation with identification of promoters and inhibitors to their growth. However, considerably more investigations are required to correlate the stone constituents with the pathophysiology of stone disease. A better understanding of the physiochemical principles underlying stone pathogenesis, growth, and inhibition requires more precise and exact knowledge of their chemical compositions. Inaccurate information would lead to wrong diagnosis for their effective cure and treatment.

Spectroscopic studies of kidney stones are important for determining the chemical constituents and structure of stones. Such compositional information furnishes additional knowledge about their pathogenesis. Regrettably, conventional urine tests, collected continuously over 24-h, are instead used to monitor the chemistry of the urine which is generally complicated, time-consuming, and non-specific (Rao et al. 2011). In our experience, quantitative analysis of kidney stones is important for effective treatment of kidney disease and also in the prevention of their recurrence.

Over the past few years, trace metal determination has gained growing interest in the field of nephrology. Analysis of

Fig. 4 General concept and steps in kidney stone formation

microelements including iron, copper, zinc, and lead have been conducted over the last three decades particularly with regard to the investigation of stone pathogenesis (Rao et al. 2011; Ramaswamy et al. 2015; Singh and Rai 2014; Słojewski 2011). Various elements have been investigated which clearly revealed their effects in the formation of different kinds of stones (Rao et al. 2011; Ramaswamy et al. 2015; Singh and Rai 2014; Słojewski 2011). Elemental analysis of these stones directs us toward areas that are more patient driven and specialized and thus have the potential to personalize treatment thereby reducing the number of procedures, direct health cost, and discomfort to patients. However, despite several studies being conducted on kidney stone composition, there is insufficient information available, particularly about the spatially distributed heavy and trace elements within these stones. Greater knowledge of elemental distribution within the stones will help in understanding the promoters and inhibitors involving in nucleation and growth of the stones and may also assist with treatment protocols, such as ultrasonic breakdown. For this reason, in the present review article, we concentrate on a number of advanced spectroscopic techniques for the detection and quantification of major and trace elements present in the kidney stones.

Current spectroscopic approaches

Advanced spectroscopic techniques are being broadly employed in various areas of scientific research including

biomedical applications including to quantify stone composition without their requisite destruction. Such techniques also allow samples to be reused for other analytical studies. In the present review article, we present typical results gained from the analysis of gallbladder and kidney stones using advanced multi-spectroscopic techniques such as Fourier transform infra-red (FTIR), ultra-violet visible (UV-Vis), wavelength dispersive X-ray fluorescence (WD-XRF), laser-induced breakdown spectroscopy (LIBS), and time-of-flight secondary-ion mass spectroscopy (TOF-SIMS). The technique and methodology of these techniques are briefly explained followed by their use and applications in gastroenterology and urology.

FTIR spectroscopy

FTIR spectroscopy is a powerful tool for identifying organic and inorganic components through the measurement of an IR absorption spectrum. It can provide qualitative information on target material composition. In addition, relevant standards can be used for quantitative analyses. FTIR has a proven capability to analyze gallstones and kidney stones and exhibits specificity, rapidity, and multi-purpose properties (Rao et al. 2011; Singh and Rai 2014 & Singh et al. 2017; Jaswal et al. 2016a, 2019). It can be used to analyze a wide range of bulk materials, thin films, liquids, solids, pastes, powders, and fibers. FTIR spectroscopy is also able to investigate cellular changes at the molecular level (Suzuki et al. 1975; Carmona

et al. 1997) and is capable of providing the chemical structure and composition of biological samples at the molecular level (Suzuki et al. 1975; Carmona et al. 1997). Due to its unique biomedical capabilities, it has become a widely used technique for clinical studies (Rao et al. 2011; Singh and Rai 2014; Singh et al. 2017; Jaswal et al. 2019). Most importantly, being reagent free, it can rapidly examine changes in the biochemical composition of cells and biological tissues (Rao et al. 2011; Singh and Rai 2014; Jaswal et al. 2019).

FTIR-based spectral analysis of stones in the frequency ranges 4000–400 cm^{-1} indicate the concentration of molecules of the target sample through reporting absorption of specific vibration bands. FTIR spectroscopy measurements are easy to perform, rapid, precise, and non-destructive in nature. They have been extensively applied to study the structure and conformation of proteins, fatty acids, carbohydrates, and nucleic acids (Singh and Rai 2014; Słojewski 2011; Suzuki et al. 1975; Carmona et al. 1997). FTIR spectroscopy has recently been employed in the field of cholelithiasis, nephrolithiasis, and urolithiasis (Singh and Rai 2014; Słojewski 2011; Suzuki et al. 1975; Carmona et al. 1997). In the present review article, examples of FTIR spectroscopy-based analysis are shown for different kinds of the gallstones and kidney stones revealing major and minor chemical compositions.

Modern FTIR spectrometers show advantages over the continuous infrared spectrometers developed in the mid-1980's. Advantages and limitations of modern FTIR devices are tabulated in Table 1.

WD-XRF spectroscopy

X-Ray fluorescence (XRF) is a useful analytical technique for the study of elemental composition of bulk materials including biomaterials due to its accuracy, precision, sensitivity, and dynamic linear range (Bielecka et al. 2014; Singh et al. 2017; Haschke 2014). It covers a broad range of elements and can handle a wide spread of weight fractions ranging from traces to pure elements. It provides elemental analysis based on measurement of emitted characteristic X-rays from the sample (Haschke et al., 2014; Beckhoff et al. 2006). With the bombardment of energetic X-rays, characteristic X-rays

are emitted from target material atoms, and these are used to evaluate the elemental composition of the sample. WDXRF is one of two general categories of X-ray fluorescence methods employed for elemental measurements that are particularly useful for bio-medical applications. In WDXRF spectroscopy, all of the elements of the sample are excited simultaneously in the WDXRF spectrometer. The different energies of the characteristic X-Ray emission from the target materials are then diffracted into different directions by an analyzing crystal. Thus, the intensities of emitted X-rays at a particular wavelength are measured using a detector at a certain angle. The use of WDXRF methods is advantageous because it provides high resolution spectra with minimal spectral overlaps (Bielecka et al. 2014). WDXRF is sensitive for nearly all elements with good limits of detection and quantification. It also minimizes the spectral overlays and provides high spectral resolution.

Figure 5 shows a schematic diagram of a typical WDXRF spectrometer. Use of WDXRF spectrometry for stone analysis is an emerging area in biomedical field (Singh et al. 2017; Jaswal et al. 2019). A variant of X-Ray fluorescence (XRF) spectroscopy in energy dispersive mode (EDXRF) has also been applied to the analysis of kidney stones (Gurol et al. 2004), and gallstones (Ekinici and Sahin 2002; Ashok et al. 2003). Ekinici and Sahin (2002) quantified the elements Ca and I in gallstone samples using EDXRF, while Ashok et al. (2003) used the technique to investigate the B, Fe, Pb, and Zn content of gallstones. However, use and application of WDXRF spectroscopy toward gallstones and kidney stones have only been reported by Bielecka et al., (2014), which motivated us to apply WDXRF for biomedical applications. In the energy dispersive mode (EDXRF), the energetic distribution of X-rays is analyzed. The spectrometers used in EDXRF have less resolution than wavelength dispersive (WDXRF) spectrometers (Haschke 2014; Jenkins et al. 1981; Beckhoff et al. 2006). Comparison between EDXRF and WDXRF including their capabilities and limitations is listed in Table 2.

In a later section, we summarize the utility of WDXRF spectroscopy for elemental analysis in gallstone and kidney

Table 1 Advantages and limitations of FTIR spectroscopy

Advantages	Limitations
<ul style="list-style-type: none"> • Throughput advantage artifacts • Multiplex advantage • Better signal to noise ratio (SNR) 	<ul style="list-style-type: none"> • Artifacts
Precise wave number measurement	
<ul style="list-style-type: none"> • Possibilities of micro-FTIR imaging of very small region of the samples 	

Fig. 5 Schematic diagram of wavelength dispersive X-ray fluorescence spectrometry (WDXRF)

stone samples of patients of different age groups, dietary habits, and geographical regions.

Time-of-flight secondary ion mass spectrometry (TOF-SIMS)

TOF-SIMS is another useful surface analytical technique for inorganic and organic materials. The working methods, principle, and different field of applications of TOF-SIMS are well described by Vickerman and Briggs (Vickerman and Briggs

2001). Typically, a pulsed particle beam consisting of either Bi_n^+ , Cs^+ , Ga^+ , or Ar^+ is employed in TOF-SIMS to dislodge secondary chemical ions from the surface of the target materials. Thereafter, secondary positive and negative ions and electrons from the surface of the target materials undergo desorption. These secondary ions from the surface are then accelerated into a flight tube, and their mass is determined by computing the exact time of their reaching onto the detector. The secondary ion mass spectra are used to determine the elemental constituents present on the surface of the sample.

Table 2 Comparison of WDXRF and EDXRF for different analysis parameters

S. No.	Parameters	WDXRF	EDXRF
1.	Mode of measurements	Multi-channel	Simultaneous
2.	Energy resolution	<ul style="list-style-type: none"> • High for low energies • Worse for higher energies 	<ul style="list-style-type: none"> • Low for low energies, • Good for high energies
3.	Signal to noise (S/N) ratio	Very good and dependent on crystal	Limited (depends on detector and electronics)
4.	Count rates	<ul style="list-style-type: none"> • High • Counting (up to 1000 kcps) 	<ul style="list-style-type: none"> • Limited by signal electronics • Up to several 100 kcps
5.	Mechanical effort	High (due to exact movement of crystal and detector, exact sample positioning)	Small (no moved parts, only sample positioning)
6.	Brightness	<ul style="list-style-type: none"> • Low (due to small acceptance angle) • High excitation intensity required 	<ul style="list-style-type: none"> • High (due to closeness of sample to detector) • Low excitation intensity sufficient
7.	Sensitivity	High	Low
8.	Data collection time	Tens of minutes	Minutes
9.	Spectral artifacts	Rare	Major ones include escape peaks, pulse pileup, electron-beam scattering, peak overlap, and window absorption effect

Furthermore, the incident beam is rastered across a particular region of the sample surface to produce chemical images (2D) of that particular area of the sample surface. In addition, a dual beam approach is used for depth profiling analysis of multi-layered samples. Nowadays, advanced TOF-SIMS instruments equipped with a powerful computer and software can be used to provide retrospective analysis permitting the construction of chemical imaging maps and spectra of specific sample regions (Vickerman et al., 2001).

TOF-SIMS is used by material scientists to study biological materials, polymers, and pharmaceutical products (Vickerman et al., 2001; Ghumman et al. 2012; Ghumman et al. 2010). It can provide chemical information on a variety of samples (including bio-samples) with molecular specificity. It has numerous advantages as compared with other existing methods with these advantages including, sensitivity to all elements, simultaneous imaging of multiple distributed elements with a spatial resolution below 200 nm. TOF-SIMS not only provides elemental information but, dependent upon the nature of the primary ion beam, can also inform on the structural and molecular properties of the target sample.

Recently, TOF-SIMS has been employed to study biomaterials such as gallstones and kidney stones. Presently, it has been employed to analyze numerous kinds of kidney stones and gallstones (Ghumman et al. 2012; Ghumman et al. 2010). Ghumman et al. (2012) analyzed cystine and cholesterol type stones using TOF-SIMS techniques. Further, Ghumman et al. (2010) have used this surface analysis technique to characterize human stones. However, in those investigations the authors did not provide the elemental or spatial information but instead concentrated on the measurement of protonated cholesterol $[M-H]^+$ in gallstone (Ghumman et al. 2012; Ghumman et al. 2010). The capabilities and limitation of TOF-SIMS is tabulated in Table 3.

Laser-induced breakdown spectroscopy (LIBS)

LIBS is an optically sensitive laser based elemental analysis technique being used to analyses solid, liquid and gaseous samples, including biological species (Cremers and Radziemski 2006; Miziolek et al. 2006; Singh and Thakur 2007; Musazzi and Perini 2014). In brief, this technique is relied on the formation of short-lived laser-induced micro-plasma following irradiation of the sample with high-power pulsed laser beam. The molecules from the target materials are dissociated into their atomic and ionic form, and the optical emission from the plasma provides the information's about the chemical constituents of the target sample. The laser-produced plasma was captured using the collecting optics (generally optical fiber bundle) and fed into the high-resolution spectrometer. Therefore, the LIBS spectra revealed the crucial information's of elements and their concentrations in the sample. It is a quite simple, rapid, and reliable atomic emission technique to inspect gallstones and kidney stones.

Mulvaney and Beck (1968) described the first in-vitro use of a continuous wave ruby laser to fragment urinary stone samples. In 1989, the first therapeutic application of lasers to stone samples was published (Hofmann et al. 1989). It was observed that the shockwaves generated by laser ablation could break stones into small particles (Hofmann et al. 1989). The first use of the LIBS technique to analyze kidney stones was described in 2005 by Fang et al. (2005). After that, Singh et al. (2009b) investigated kidney stones using LIBS technique. Nowadays, this technique has emerged as an optimal technology to analyze gallstones and kidney stones with a proven capability for clinical application in the diagnosis of nephrological and gastroenterological disorders. In the present review article, we provide examples of the use of the LIBS technique to analyze gallstones and kidney stones.

Table 3 Capabilities and limitations of TOF-SIMS

Capabilities	Limitations
<ul style="list-style-type: none"> Investigation of all masses on sample surfaces including positive and negative ions, isotopes, and molecular components Elemental and chemical imaging maps at sub-micron scale High mass resolution Highly sensitive for trace elements and compounds (~ ppb level) Possibilities of investigation of insulating and conducting materials Depth profiling analysis (up to 10s of nanometers) Non-destructive analysis Possibility of retrospective analysis for post-data acquisition analysis and explanation of stored spectra 	<ul style="list-style-type: none"> Produce semi-quantitative results Optical capabilities are limited Problem of charging in some samples, although charge compensation routines are generally sufficient to overcome these problems Possibility of image shifting while changing from positive to negative ion data collection mode and hence difficult to collect positive and negative ion data on exactly the same spot Too much data (every pixel of an image produced by ToF-SIMS contains a full mass spectrum and take hours, days or weeks for complete analysis of data)

Advantages and limitations of LIBS technique has been previously described in detail (Cremers and Radziemski 2006; Miziolek et al. 2006; Singh and Thakur 2007; Musazzi and Perini 2014). The LIBS analysis process is quick and can be utilized for any kind of samples regardless of their physical states. It has been found very useful for in situ trace elemental profiling of real samples. LIBS has the following merits over other analytical techniques:

- It does not require any kind of sample preparation unlike atomic absorption spectroscopy (AAS) and inductively coupled plasma-atomic emission spectroscopy/mass spectroscopy (ICP-AES/MS).
- A small amount of sample ($\sim \mu\text{g}$) is used to create plasma, which makes it minimally destructive.
- It is very fast analytical technique and thus, LIBS measurements are performed within a fraction of a second.
- It is especially sensitive to lighter elements such as C, H, N, O, and Li which is not possible to detect with other techniques.
- No direct access to the sample is required.
- It can be coupled with other techniques such as Raman spectroscopy, ICP-OES, etc. for multi-elemental and molecular surface analysis.

Analyzing gallstones and kidney stones employing advanced spectroscopic techniques

In recent years, elemental analysis techniques such as XRF, TOF-SIMS, and LIBS have gained much attention for stone analysis due to their unique inherent properties. FTIR spectroscopy is also a well-established molecular analysis method to classify stones based on their chemical compositions. Applications of FTIR, XRF, TOF-SIMS, and LIBS methods have been used in medicine for diagnosis. In the following subsections, the most recent developments and future prospects of FTIR, XRF, TOF-SIMS, and LIBS techniques to analyze stone samples, in the field of gastroenterology and nephrology, have been elaborated.

Studies on stones using FTIR spectroscopy

FTIR spectroscopy is a well-recognized, rapid, and convenient technique to characterize gallstones and kidney stones, which is applicable to all kinds of stones irrespective of their crystalline nature and requires only a small amount of sample. At present, no single technique is capable to identify and characterize all aspects of the gallstone and kidney stone components, and therefore, a quick, cost-effective, minimally destructive investigation workflow has to be established.

FTIR has been applied successfully to examine the major chemical constituents of gallstones and kidney stones such as cholesterol, calcium bilirubinate, and calcium carbonate/phosphates (Trotman et al. 1977; Trotman 1991; Kaufman et al. 1989; Kaufman et al. 1994). Its application in the field of gastroenterology and nephrology has rapidly expanded and has been shown to provide accurate and rapid results. IR spectroscopy has also been used to demonstrate that bilirubin in gallstones is present as a calcium salt rather than as a protonated acid (Trotman et al. 1977). Regardless of inconsistencies in the color-based classification of brown and black pigment stones, FTIR spectroscopy can reliably differentiate different varieties of pigmented stones (Malet et al. 1988; Trotman 1991; Kaufman et al. 1989; Kaufman et al. 1994; Weissman et al. 1959; Chihara et al. 1960).

Raha et al. (1967) and Peuchant et al. (1987) used the IR technique to analyze human gallstones and quantified the levels of cholesterol, calcium carbonate, and calcium bilirubinate. A spectroscopic investigation on the formation mechanism of pigment gallstones by Wu et al. (1997) showed that black pigment gallstones are found mainly in Western countries whereas in China, it is only 3%. Laloum et al. (1998) subsequently reported a FTIR-based comparative account of all these gallstones. Such FTIR spectral studies of human gallstones were also compared by Laloum et al. (1998).

Traditional approaches to gallstone analyses and classification includes visual inspection, chemical analyses, and physical analyses. However, the classification of gallstone based on their appearance is associated with problems of subjective analyses. To improve the analyses of gallstone, a chemical approach can be used; however, it is very labor-intensive and has poor sensitivity which leads to underestimation of cholesterol and insoluble residues (Trotman et al. 1977; Gokulakrishnan et al. 2001; Toyada 1966; Tandon 1988). Gokulakrishnan et al. (2001) has determined the composition of gallstones in South India by comparing visual assessment with spectral interpretation of Infrared spectra. FTIR spectroscopy is one of the best methods for analyzing crystalline, non-crystalline, organic, and inorganic constituents, i.e., irrespective of sample (Kothai et al. 2009).

The major components of human gallstones are cholesterol and bilirubin. Other compounds that have been found in gallstones include calcium carbonate, calcium phosphate salts, calcium bilirubinate, fatty salts, various cholic acid derivatives, polysaccharides, and proteins (Liu et al. 2002). The brown pigment in gallstones has been dissolved in various solvents such as chloroform, ethanol, ether, hydrochloric acid, and its spectra recorded using the FTIR method. The results show that insoluble compounds of bilirubin, bilirubinate salt, and proteins are present. The FTIR technique shows great utility for the determination of these components even when only very small amounts of material are available for analysis.

Chandran et al. (2007) studied the chemical compositions of human gallstones using the FTIR method and performed quantitative analyses of cholesterol, total bilirubin, fatty acids, triglycerides, phospholipids, bile acids, and soluble proteins. Recently, Kleiner et al. (2002) performed comparative studies of gallstones from children and adults using FTIR spectroscopy and fluorescence microscopy. Weerakoon et al. (2015) have used the FTIR method for chemical characterization of gallstones of the patients in Sri Lanka. The authors demonstrated the presence of different calcium salts such as calcium bilirubinate, calcium carbonate, and calcium phosphate in stone samples collected from middle-aged female patients of Kandy district of Sri Lanka. They found that the majority of these gallstones were either pigment or mixed cholesterol with a pigment nidus, denoting the possible role of elevated unconjugated bilirubin in bile on the pathogenesis of stones.

Recently, Cavalu et al. (2015) used a series of highly sensitive techniques such as SEM, FTIR, EPR spectroscopy, and XRD along with biochemical analysis to investigate factors involved in the pathogenesis of gallstones. The authors identified a macromolecular network structure involving proteins in complex with a bilirubin-coordinated polymer. They concluded that bilirubin and bilirubinate free radical complexes play an important role in pigment gallstone formation. Recently, Cheng et al. (2016) reported spectral and morphological classification of different chronic and acute Taiwanese gallstones via FTIR, SEM, and ESEM-EDX microanalyses. Very recently, Ha and Park (2018) used FTIR spectroscopy and photography to classify the gallstone samples based on the pattern of their characteristic FTIR absorption bands.

In a series of studies, Jaswal et al. (2015a, 2015b, 2016b, and 2019) performed spectroscopic studies to investigate elemental compositions of different kinds of gallstones. Before performing elemental studies, the authors used the FTIR technique to classify gallstone samples into different categories (cholesterol, mixed and pigment type). Using the FTIR technique, Jaswal et al. (2016a) clearly distinguished cholesterol type gallstones from pigment type gallstones. Figure 6 shows the typical FTIR spectra of cholesterol (G1, G2) and pigment type (G3) gallstones used in that study. The authors also observed the different level of cholesterol and bilirubin in mixed type gallstones.

Infrared spectroscopy and chemical analysis are the most common techniques for routine analysis of kidney stones in order to identify amorphous and non-crystalline materials and drug metabolites. These compounds are not easily detectable using other molecular analysis techniques (Lehmann et al. 1988). Carmona et al. (1997) have reviewed the use and application of infrared and Raman spectroscopic techniques in urology and discussed their relative efficiency and adaptability to routine analysis.

Bazin et al. (2012) used the FTIR method to analyze kidney stone with particular focus on the spatial distribution of components within them (starting from center to surface) using the radial distribution to help date the deposition in a manner similar to the analysis of elements in tree rings. The authors observed the presence of calcium oxalate monohydrate (whewellite) and ammonium urate which is induced by “diarrhea” in the center part of the kidney stone. In the surface parts of kidney stone, they observed the presence of carbonated apatite and calcium oxalate dehydrate (weddellite) the production of which is correlated to hypercalciuria. Bhatt and Paul (2008) employed the FTIR method to study kidney stones and found that calcium oxalate was a major chemical constituent of kidney stones with the presence of separate phases of hydroxyl and carbon apatite. Some authors have conducted FTIR studies of kidney stones using very large sample sizes (Volmer et al. 2001; Estepa and Daudon 1997). In a variant of the technique, Gulley-Stahl et al. (2009) quantitatively investigated urinary stone components by using attenuated total internal reflection (ATR)-FTIR.

Paluszkiwicz et al. (1997) used FTIR and FT-Raman spectroscopic techniques for structural studies of kidney stones and proton induced X-ray emission (PIXE) and atomic emission spectroscopy (AES) techniques to determine their elemental concentrations. The authors were able to correlate their structural and elemental studies and linked with each other. Nguyen and Daudon (1997) also used IR and Raman spectroscopy to analyze kidney stones and concluded that this combination of spectroscopic techniques represented the best possible approach for the identification of kidney stones. The authors' conclusions were based on simplicity, ease of use, rapid implementation, and requirement for minimal sample quantity. XRD and IR spectroscopy have also been successfully used for kidney stone analysis (Rebentisch 1993; Hesse et al. 1972; Schneider et al. 1973). Recently, Charafi et al. (2010) studied a large number of kidney stones using SEM and FTIR techniques and clearly revealed the predominance of whewellite (54%), weddellite (13.5%), purines (24.3%), and struvite (8.1%). Recently, Siener et al. (2016) conducted a European-based multi-laboratory study to compare results gained using FTIR method in combination with XRD for assessment of urinary stone analysis. In this study, nine laboratories from eight European countries participated in six quality control surveys for urinary calculi analyses of the Reference Institute for Bioanalytics, Bonn, Germany, between 2010 and 2014.

Recently, Gilad et al. (2017) used FTIR in combination with chemical analysis and XRD as a means for cross-validating results gained using these separate techniques. Khan et al. (2018) used FTIR spectroscopy to analyze 449 kidney stone samples received from patients undergoing surgery in an age group spanning 1 to 81 years old and compared results gained using FTIR spectroscopy with chemical

analysis results. In adults, the calcium oxalate stone type (calcium oxalate monohydrate, COM) was the most common crystal, followed by uric acid and calcium oxalate dihydrate (COD). In children, the most frequently occurring type was predominantly calcium oxalate dihydrate, followed by COM, ammonium urate, carbonate apatite, uric acid, and cystine. Core composition in most of the stones showed ammonium urate, COM, and carbonate apatite in some stones, while uric acid crystals were detected by FTIR. In their study, they were able to demonstrate that FT-IR analysis could overcome many limitations associated with chemical analysis.

Recently, Sekkoum et al. (2016) reported the usefulness of FTIR spectroscopy technique in the study of biochemical composition of stones in the south west of Algeria. The authors analyzed different layers of urinary stones and confirmed that calcium oxalate monohydrate and dehydrates are the main components of urinary stones. They have also found that the external layers of majority of stones are mainly composed of calcium oxalate monohydrate (whewellite) particularly in female gender (65%). Daudon et al. (2016) used XRD and FTIR techniques to analyze urinary stone which allowed accurate identification of the chemical nature, crystalline phases, and relative proportions of stone constituents. These authors were able to conclude that the morpho-constitutional analysis of urinary stones which combines careful morphologic examination of the surface and section of stones with an analysis of their composition by means of FTIR or XRD gave considerable insight into the etiology of kidney stone disease. Tonannavar et al. (2016) demonstrated how IR spectroscopy in combination with Raman spectroscopy could accurately identify mineral constituents in kidney stones. The identified mineral components include calcium oxalate monohydrate (COM, whewellite), calcium oxalate dihydrate (COD, weddellite), magnesium ammonium phosphate hexahydrate (MAPH, struvite), calcium hydrogen phosphate dihydrate (CHPD, brushite), pentacalcium hydroxy triphosphate (PCHT, hydroxyapatite), and uric acid (UA). D'Alessandro et al. (2017) employed FTIR technique to investigate the stone's composition of a group of Sicilian children, and authors further performed metabolic studies in order to formulate the correct diagnosis and establish therapy.

In a recent study by Oliver et al. (2016), IR vibrational spectroscopy has been demonstrated as a rapid and novel diagnostic and monitoring tool for cystinuria, and thus, IR spectroscopy have proven its potential applications in nephrology. We have not covered all the reports of FTIR spectroscopy to gallstones and kidney stones; however, we have tried to cover references indicating the major aspects of its use in gastroenterology and nephrology. Literature reports reveal strong evidence in favor of FTIR spectroscopy for its use and application to classify gallstones and kidney stones and in the analysis of their chemical constituents.

Studies on stones using XRF spectrometry

X-ray fluorescence (XRF) is considered as a fast and nondestructive technique for qualitative and quantitative analysis of elements in the range from beryllium to uranium without the requirement for standards in powdered, solid, or liquid specimens. The method is extremely useful for analyzing basic elements in a sample with an accuracy of 0.1% (Jaswal et al. 2019; Haschke 2014). The lower limit of detection of trace elements is in the range from 0.1 to 10 ppm (Haschke 2014; Beckhoff et al. 2006).

Application of XRF spectrometry in stone diseases is an emerging area. X-Ray fluorescence spectroscopy in energy dispersive mode (ED-XRF) has been applied to analyze gallstones (Bielecka et al. 2014; Ekinici and Sahin 2002). Ekinici and Sahin (2002) quantified Ca and I of gallstone samples using this technique. Ashok et al. (2003) also used EDXRF to measure Br, Cu, Fe, Pb, and Zn present in gallstones. Al-Kinani et al. (1984) used the XRF technique together with neutron activation (NA), proton induced X-ray emission (PIXE) to analyze minor and trace elements such as Ca, P, S, Al, Mn, Cu, and I in gallstone and bile samples. The distribution and form of Ca was examined qualitatively by scanning-electron microprobe and IR spectroscopy. Suvorova et al. (2017) reviewed the combined use of a number of analytical techniques such as fluorescence microscopy, XRF spectroscopy, NA analysis, PIXE, AAS, gamma-ray spectrometry, and electron paramagnetic resonance (EPR). Ramya et al. (2017) used the EDXRF technique for comparative chemical and structural analysis of gallstones collected from patients residing in the northern and southern parts of India, respectively. Used in combination with physicochemical methods such as XRD, IR spectroscopy, SEM and CHN analysis, thermal analysis, and NMR spectroscopy, the elements C, N, O, Ca, S, Na, Mg, and Cl were detected in gallstone samples with differences noted between these two samples.

Athanasiadou et al. (2013) studied cholesterol gallstones from patients located in England and Greece using XRF, XRD, FTIR, and NMR including SEM-EDS. The authors reported the morphology of cholesterol microcrystals by means of SEM-EDS. Using the XRF technique, the authors found Ca as the dominant non-organic metal in all gallstones together with Fe, Cu, Pb, and Ni. Sharma et al. (2015) analyzed a large number of gallstone samples using FTIR, ICP-OES, TGA, and SEM-EDX techniques. The authors observed that pigment gallstones were predominately occurred in multiple forms, cholesterol as solitaire and black pigment as slug. Using TGA technique, the authors found pigment stones more thermally stable than cholesterol stones.

Recently, Jaswal et al. (2015a, 2019) used WD-XRF spectrometry to study a large number of gallstone samples of patients from different age groups, geographical regions, and

dietary habits and quantified the major, trace, and heavy metals in gallstones. The results suggest a prospective role for WD-XRF spectrometry (together with FTIR spectroscopy) in the development of a quantitative gastroenterology research. The authors compared their results with existing literature values reported using WD-XRF spectrometry on gallstones. With the WD-XRF technique, different types of elements namely, calcium, magnesium, manganese, zinc, sodium, copper, iron, phosphorous, sulfur, silicon, chlorine, aluminum, palladium, and ruthenium were detected and quantified in gallstone samples. Typical gallstone WDXRF spectra are shown in Fig. 7 with the different energy ranges reflecting the different compositions of major, trace, and heavy elements. The authors reported that Pd and Ru were detected in gallstones samples using WD-XRF, suggesting a possible role in gallstone formation. Different parts of the gallstones have different colors (often brownish and black). FTIR analysis showed the presence of bilirubin whereas WD-XRF analyses showed the presence of Ca, Cu, and other elements in gallstone samples. This clearly revealed the presence of Ca and Cu in the form of bilirubinate salts that are largely responsible for the brownish and black colors of the central part of gallstones. Bazin et al. (2007) employed the XRF technique to quantify Cu, Fe, Pb, Rb, Se, Sr, and Zn in calcium oxalate, calcium phosphate, struvite, uric acid, cystine, and mixed type urinary stones. Srivastava et al. (2012) employed INAA and EDXRF techniques to quantify Ca, Na, K, Mn, Co, Cr, Zn, Br, and Sm in kidney stones taken from Indian

patients. The same group (Srivastava et al. 2014) also applied instrumental neutron activation analysis (INAA), EDXRF and XRD techniques to analyze kidney stones extracted from Indian patients. Particularly, EDXRF was employed to investigate the level of Ca in stones. Gurol et al. (2004) quantified the elements Ca, K, Cl, P, and S present in kidney stones using EDXRF spectroscopy. Moroz et al. (2009) utilized synchrotron radiation (SRXRF) in order to measure microelements and minerals of kidney stones. Using XRF spectroscopy, Dessombz et al. (2016) detected Al and Si in kidney stones to show their existence in aluminosilicate phases. Bielecka et al. (2014) employed the WDXRF technique to perform elemental analysis of O, Na, Mg, Al, Si, P, S, Cl, K, and Ca in kidney stones. The authors were also able to detect elements such as Fe, Cu, Zn, Br, Sr, and Pb in kidney stones using TXRF spectroscopy.

Abboud (2008) employed the XRF technique to measure the concentrations of the major element Ca and trace elements like Ba, P, Fe, S, Zr, Mo, Cu, Co, and F ranging from 1.56 to 4.63% in calcium oxalate and calcium phosphate type urinary stones of Jordanian patients. A good correlation was found between elemental concentrations and such factors as water intake, climate conditions, protein rich foods, and certain drugs. Blaschko et al. (2013a) applied synchrotron radiation based micro (μ)-XRF, X-ray absorption, and XRD advanced imaging techniques to identify and map the elemental composition, including trace elements, of urinary calculi on a μ m scale. The same group (Blaschko et al. 2013b) measured the

Fig. 6 FTIR spectra of gallstone samples (G1, G2, G3). Figure adapted from Jaswal et al., *Lasers Med. Sci.*, 31, 573–579, 2016, with the permission from Springer Nature

elements Ca, Fe, Pb, Sr, and Zn in calcium oxalate, brushite, uric acid, and mixed type kidney stones using XRF spectroscopy. Recently, Oztoprak et al. (2012) used LIBS, XRD, and XRF technique to analyze the heterogeneity of kidney stones. In this study, the authors observed the ratio of hydrogen (H) and carbon (C) as an important indicator of organic compounds such as uric acid present in kidney stones. The authors also detected minor elements such as P, S, Si, Ti, and Zn in the kidney stones. Kubala-Kukus et al. (2017) reported the application of total reflection X-ray fluorescence (TXRF) and X-ray powder diffraction (XRPD) techniques to determine the elemental and chemical composition of human kidney stones. The authors detected elements such as P, K, Ca, Fe, Zn, Ni, Br, Sr, and Pb were in all kinds of kidney stone samples. They have also detected some other elements such as Mg, S, Cl, Ti, V, Cr, Mn, Cu, Se, Rb, I, and Bi in kidney stones (censoring effect). Using XRPD method, the authors detected some crystalline substances such as apatite, struvite, uric acid, weddellite, whewellite, magnesium phosphate, and calcium phosphate, and this information was used to classify the kidney stone samples in four groups.

Carpentier et al. (2011) performed an investigation on a set of Randall's plaques (RP), extracted from human kidney stones, using μ -XRD and μ -XRF analyses in order to determine the chemical composition of the plaque as well as the nature and amount of trace elements. The authors showed that Zn levels are dramatically increased in carapatite of RP by comparison to carapatite in kidney stones, suggesting that calcified deposits within the medullar interstitium are a pathological process involving a tissue reaction.

Singh et al. (2017) analyzed kidney stone samples after classifying them by an FTIR spectroscopy-based assessment of their chemical composition, particularly oxalate type (KS1, KS3-KS5) and struvite type (KS2) stones.

Figure 8 shows a typical WD-XRF spectrum of struvite type kidney stones (KS2) indicating the presence of a characteristic elemental signature. Employing WD-XRF spectrometry, a wide range of elements in the different kinds of kidney stones were determined with these including calcium, magnesium, phosphorous, sodium, potassium, chlorine, sulfur, silicon, iodine, titanium, iron, ruthenium, zinc, aluminum, strontium, nickel, copper, and bromine. Using WDXRF, they detected very low levels of Ru in kidney stones. The relative content of elements present in different types of stones was shown to be different. Figure 9 indicates the relative concentration of elements in oxalate type and struvite type stones which suggests that the formation mechanism of both the stones may be quite different.

Taken in toto these experimental observations suggest that WD-XRF is a powerful analytical technique applicable to diagnose nephrological and gastroenterological disorders.

In the present article, we have reviewed the utility of WDXRF spectroscopy to detect numerous heavy and trace

metals including carcinogenic heavy metals in gallstones and kidney stones collected from patients of different age groups, geographical regions, and dietary intake.

Studies on stones using TOF-SIMS spectrometry

TOF-SIMS has gained much interest for the study of biomaterials and has been employed to analyze numerous types of kidney stones and gallstones (Ghumman et al. 2012; Ghumman et al. 2010). Ghumman et al. (2012) analyzed cystine and cholesterol type stones using TOF-SIMS techniques. Ghumman et al. (2010) used this mode of surface analysis to identify human stones; however, they did not provide information on trace element amounts nor their spatial distribution. Rather, the authors instead measured the protonated molecular forms of cholesterol $[M-H]^+$ in gallstones.

TOF-SIMS (VG Ionex IX23LS with upgraded data acquisition and control system) was used by Ghumman et al. (2013) to study urinary stones along with reference samples of calcium oxalate (CO) and calcium phosphate (CP). Reliable identification of CP levels was achieved using positive SIMS mode on basis of the PO^+/POH^+ and $CaPO_2^+/Ca_2O^+$ peak ratios. Within urinary stones, they successfully distinguished pure calcium oxalate (a major component of urinary stones) from calcium phosphates by showing the presence of its characteristic ion peaks. Ghumman et al. (2011) also used TOF-SIMS to identify calcium formate $Ca(HCO_2)_2$ and metabolite of vitamin B₆ in human kidney stones.

Sodhi et al. (2011) employed ToF-SIMS for the imaging of the microstructure of different kidney stone samples. This data indicated that the melamine-induced stones were formed by different mechanisms. However, information obtained using other techniques is also required to correlate the detailed differences in the microstructure of the stone samples with the formation mechanism. It is pertinent to mention that relatively few studies (Ghumman et al. 2010, 2011, 2012, 2013) have been reported on the use and application of TOF-SIMS on human stones.

Jaswal et al. (2015b) analyzed the different parts of cholesterol type gallstones employing TOF-SIMS, employing 2D (two-dimensional) elemental images for the assessment of mineral distribution. The authors were able to analyze and obtain the data from $200 \times 200 \mu m^2$ of the area of stones. These 2D elemental spectra revealed higher elemental contents in the center part of cholesterol stone than that recorded from the surface part of the stone. Relative concentrations of all the elements (major, trace and heavy) in different parts of the stone were investigated by the authors. The TOF-SIMS surface analysis technique provided precise and reliable results and was shown to be a user-friendly measurement tool not requiring of special sample preparation as compared with the other analytical tools such as AAS and ICP-MS. This

Fig. 7 Typical wavelength dispersive X-ray fluorescence spectra of gallstones (GS1–GS5) in different energy region from (a) 0.25 to 0.75 keV indicating the presence of C and O; (b) 0.5 to 1.5 keV for the presence of O, Na, and Mg; (c) 1.8 to 3.2 keV for the presence of P, S, and Cl; (d) 3.26 to 4.26 keV for the presence of K and Ca; and (e) 5 to 18 keV for the presence of Br, Cu, Fe, Mn, K, and Sr. Figure adapted from Jaswal et al., X-Ray Spectrom., 48, 178–187, 2019, with the permission from Wiley & Sons Inc.

technique has proven its inherent worth for investigating small (micron-sized) areas of stone samples.

Studies on stones using LIBS technique

In the first study of its kind, Singh et al. (2009a) employed the LIBS technique for the qualitative analysis of chemical constituents of cholesterol gallstones using a nanosecond Nd:YAG laser beam of wavelength 532 nm with a pulse repetition rate at 10 Hz under good signal-to-noise (S/N) ratio and signal-to-background (S/B) ratio condition. The authors analyzed the center and shell parts of stones, detecting the elements Ca, C, Cu, H, Mg, N, Na, O, and K. Despite its distribution in other areas, Cu was not detected in the surface parts

of the cholesterol gallstones. Higher levels of Ca, Cu, and Mg are in the center part of the stones than that from the shell parts. Along with that, the content of Na and K were found at higher levels in the non-pigmented part than in the pigmented part, which indicated their role in pigmentation. Furthermore, Singh et al. (2008) used LIBS technique to study pigmented, cholesterol, and mixed gallstones based on their major and trace chemical constituents. They used calibration-free (CF) LIBS method to calculate concentrations of these elements present in the gallstones and also compared their results with the results obtained from ICP–AES. The authors also employed the LIBS technique for the cross-sectional study of kidney stones in order to predict the variation of elemental concentration across the width of the stones. On

Fig. 8 A typical WD-XRF spectra of struvite stone (KS2) obtained from WD-XRF spectrometer. Figure adapted from Singh et al., *X-Ray Spectrom.*, 46, 283–291, 2017, with the permission from Wiley & Sons Inc.

the basis of these observations, they speculated about the possible roles of different elements found within stones and their differential effects upon stone formation.

Pathak et al. (2012) employed the LIBS technique to characterize cholesterol and pigment gallstones based on their atomic lines appeared from different elements and C_2 Swan molecule bands in the LIBS spectra. The authors used principal component analysis (PCA) method on the LIBS data of stones to classify the gallstone samples. Further, the same group (Pathak et al. 2012) also studied gallstone samples (collected from patients residing in the northeast part of India) using the LIBS technique. For this, LIBS spectra of the different layers of the gallstones were recorded in the spectral region 200–900 nm to analyze the behavior of Ca, Mn, Mg, Cu, Si, P, Fe, Na, and K. In this study, lighter elements such as C, H, N, and O were also measured in gallstones. They correlated the presence of elements in the analyzed gallstones with the common diet of the general population of northeast part of India.

Unnikrishnan et al. (2015) carried out experiments using the LIBS technique on calcified tissues (teeth as well as gallstones) in order to investigate trace elements and their mapping. Recently, Gondal et al. (2016) developed a laser sensor based LIBS technique for the measurements of heavy metals Cr, Pb, Cd, Ni, and Hg in gallstones. The concentrations of these heavy metal elements were further compared with ICP data. Jaswal et al. (2016a) performed spectroscopic studies of heterogeneous cholesterol and pigmented type gallstones using the LIBS technique and verified the data using the WD-XRF method.

The application of LIBS for urinary stone analysis has been shown to be a useful in-situ method of investigation. Several LIBS researchers have attempted to correlate the trace elemental content and distribution with the mechanisms of stone formation. Hofmann et al. (1989) was the first to apply laser pulses for the analysis of kidney stones. Fang et al. (2005) used the technique to analyze the major and trace elements (Ca, Mg, Na, Sr, K, and Pb) in kidney stones concentrations of element different in different kinds of stones showing that LIBS could be used for routine clinical applications in the diagnosis of urological disorders.

Recently, Singh et al. (2009b) used LIBS to quantify Cu, Mg, Sr, and Zn in kidney stones with the use of calibration curves. They also investigated the center, shell, and the surface parts of the stone samples. The results obtained using LIBS technique was verified with data obtained by ICP-MS. They quantitatively demonstrated that calcium was a major elemental constituent of kidney stones. The authors also studied the cross-sectional variation of Ca, K, and O in kidney stone samples (Fig. 10). Potassium (K) was found at higher concentrations in center part vs. shell and surface parts of the stones while Ca and O remain at constant levels throughout the other major matrix regions of the stones.

Anzano and Lasheras (2009) studied different types of kidney stones using LIBS technique. Recently, Oztoprak et al. (2012) performed multi-technique (XRD, XRF, and LIBS) investigations on a set of kidney stones. To classify the stone samples, they carried out a chemometric analysis using principal component analysis (PCA) and partial least square-discriminative analysis (PLS-DA) methodologies. In a variation of the

Fig. 9 Relative concentration of some of the elements of oxalate type and struvite stones. Figure adapted from Singh et al., X-Ray Spectrom., 46, 283–291, 2017, with the permission from Wiley & Sons Inc.

technique, Štěpánková et al. (2013) used different laser ablation (LA)-based techniques such as simultaneous LIBS and LA-ICP-OES; LA-LIBS to investigate kidney stones.

Khalil et al. (2015) investigated kidney stone samples using LIBS technique and measured the concentration of carcinogenic elements Cd, Zn, Ca, Cr, P, Pb, and V

along with trace metals such as Ca, P, Zn, Ni, and V. Figure 11 a–c shows the LIBS spectra of a kidney stone sample indicating the presence of these elements in different wavelength regions 360–440, 620–700, and 720–800 nm. The authors were able to obtain very low limit of detection and measured the trace amounts of Zn, Ca, Cr, P, Cd, and Pb concentration in 10–19 ppm range

Fig. 10 LIBS spectra from the center, shell, and surface of the first kidney stone. Figure adapted from Singh et al., Lasers Med. Sci., 24, 749–759, 200, with the permission from Springer Nature

Fig. 11 SP-LIBS spectra showing different chemical elements present in the kidney stone sample in the (a) 360–440, (b) 620–700, and (c) 720–800 nm wavelength regions. Figure adapted from Khalil et al., Appl. Opt., 54, 2123–2131, 2015, with the permission from Optical Society of America

with their optimized SP-LIBS system. They also compared the LIBS data with ICP data and found good agreement. The authors also studied plasma parameters such as electron temperature and density for SP-LIBS system along with their dependence on incident laser energy and delay time. Figure 12 shows the temporal

evolution of electron density (N_e) for three different kidney stones. The authors concluded that LIBS is a suitable technique to analyze stone samples for both qualitative and quantitative assessment and was particularly user-friendly due to the fact that it is not requiring of any sample preparation.

Fig. 12 Temporal evolution of electron density (N_e) for three different kidney stones. Inset, Stark broadening profile of the atomic transition line of Ca(I) at 422 nm used to estimate the electron density. Solid points represent the experimental data and the smooth curves are the Lorentzian fits. Figure adapted from Khalil et al., Appl. Opt., 54, 2123–2131, 2015, with the permission from Optical Society of America

Conclusion and future prospects

In the present review article, we have discussed the potential utility of FTIR, WDXRF, TOF-SIMS, and LIBS technique for routine clinical application in stone-based urological and gastroenterological disorder diagnosis. Wide varieties of stone samples have been previously studied and their elemental contents measured and correlated against pertinent patient clinical details. These techniques are capable of providing detailed elemental profiles of stone samples and therefore assist with the generation and testing of hypotheses of stone formation on the basis of solid experimental data. The use of advanced statistical methods together with these techniques is expected to play a major future role in discrimination and characterization of biological samples like gallstones and kidney stones.

Development and use of micro-scale analysis techniques (such as μ -FTIR and μ -XRF) imaging enables visualization and mapping of the distributions of organic matter and minerals on a micrometer scale in stones samples thereby enabling deeper understanding of stone heterogeneity. To the best of our knowledge, application of μ -FTIR for the analysis of stone samples has not been reported in literature. Similarly the use of μ -XRF for the study of stones has not yet been applied in the gastroenterology and nephrology fields. The μ -XRF could prove valuable in the study of large sample sizes especially if automated elemental mapping can be applied to uncover the spatial distribution of elements within the different layers of stones. Joint use of μ -XRF with other techniques will enable identification of the factors affecting the pathogenesis of stones. This Review has discussed the capability of TOF-SIMS to analyze stone samples. This technique may be employed for depth profiling imaging (3D) of all kind of gallstones and kidney stones and also to study the different layers of stones to elucidate their pathogenesis. This latter type of applications of TOF-SIMS for 3D imaging of stone samples has not yet been published. Advances in the LIBS technique, suggest that in vivo analysis of stones employing LIBS may be feasible in the near future. Application of the LIBS technique for elemental analysis is a growing area in the biomedical field. This Review has outlined recent LIBS work related to enhanced LIBS-based analysis of gallstones and kidney stones when applied in combination with chemometrics, principle component analysis, and artificial neural networking.

In summary, the application of FTIR, XRF, TOF-SIMS, and LIBS to stone research has so far provided important quantitative information. Further biomedical research into the therapeutic and diagnostic use of spectroscopic techniques is still needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by the any of the authors.

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