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Major and Trace Elements in Human Kidney Stones: A Preliminary Investigation in Beijing, China

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Abstract: Kidney stone disease affects people globally, with its prevalence on the rise. Given the importance of elements' function in formation of kidney stones, this study investigated major and trace element content in thirty kidney stone samples from patients in Beijing. The kidney stone samples included inorganic components (calcium oxalate and carbonate apatite) and organic components (uric acid). Results showed that Ca is much higher in inorganic components than organic components. Compared to inorganic components, uric acid has a very low content of elements except for Cu and Se, which may be derived from the liver. Carbonate apatite stones have a higher element content (such as Na, K, Sr, Zn, Rb, Ba, Li, and Ti) than calcium oxalate stones, especially enrichment of Mg. The principal components analysis (PCA) extracted three principal components (PCs) with total variances of 91.91%, including the PC1 (45.08%): Na-Li-Ti-Ba-Sr-Zn, PC2 (30.05%): Rb, K, Mg, and PC3 (16.78%): Cu-Se, indicating that there are co-precipitated processes of these elements by their specific properties. A different distribution of stone types in the three components indicates a significant discrepancy in their element content, which can be an essential reference for patient intake elements.

Keywords: kidney stones; calcium oxalate; trace elements; elemental compositions; China

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1. Introduction

Kidney stone disease is a common disease affecting human health globally. As countries industrialized, kidney stone diseases became more prevalent [1]. Since the 1990s, people suffering from kidney stone has risen from 5% to 10% of the population [2]. Kidney stones can cause patients extreme pain, and further hurt renal function with permanent kidney damage [3,4]. However, there are still questions about the etiology and element behaviors of kidney stone production [5,6]. Generally, pathological biomineralization causes kidney stones [7], and they are mixed by one or more complicated components, such as calcium oxalate, calcium phosphate, and uric acid [8,9]. The formation of kidney stones is directly affected by geological conditions, diet habits, and hydrological circumstances such as water hardness by previous studies [1,10–13]. Various processes are associated with kidney stone production, all of which cause ionic constituents to be supersaturated, forming specific stones [1]. Therefore, examining kidney stones from elemental perspectives is necessary to deduce their pathophysiology, and develop future techniques for their treatment and prevention.

In recent years, the relevance and function of major and trace elements have garnered considerable interest in biominerals [10–13]. Previous studies have detected chemical elements using X-ray spectral microanalysis, suggesting that a few elements have an effect on the formation and growth of kidney stones [14,15]. Elements can accelerate or interfere nucleation of crystals by an affinity for crystalline surface [16,17]. Furthermore, the chemical and mineralogical analysis in kidney stones provides efficient information

for correct diagnosis [18]; for example, lead is always considered related to environmental contamination [19]. Therefore, this study reported the major and trace element of different types of kidney stones from patients in Beijing, and explored relationships among elements to further provide suggestions for patient intake elements according to their stone types.

2. Materials and Methods

Urologists gathered kidney stone samples during 30 patients' removal surgeries at Peking University Third Hospital. Prior to the trial, the ethical review board at the same hospital granted clearance. Prior to surgery, patients signed a written permission form that included their information. The detailed information, such as gender and age, is presented in Table S1 and the statistical results are in Table 1. All experiments, such as cleaning and dilution, were performed with ultrapure water (18.2 MΩ·cm, Cascada™, Kirkland, WA, USA). All sample stones were rinsed with ultrapure water, and 20 min water bath was conducted to clean the blood clots and residuals in the samples; then, samples were air-dried on sterile gauze before being transferred to dry vials. Sterile agate mortar and pestle were used to grind the stones after air-drying. The mineralogical compositions, including calcium oxalate (CO), carbonate apatite (CA), and uric acid (UA) were obtained through infrared spectroscopy (LIIR-20, Lambda Scientific, Vancouver, BC, Canada).

Table 1. Statistical results of major and trace elements in different kidney stones.

Kidney Stone Type	Parameters	Ca	Mg	Na	K	Sr	Zn	Li	Ti	Cu	Se	Rb	Ba	Pb
		%	mg/g	μg/g	μg/g	μg/g	μg/g	μg/kg	μg/kg	μg/kg	μg/kg	μg/kg	μg/kg	μg/kg
CO (*n* = 19)	Min	15.99	0.13	1295.53	0.01	30.84	16.89	0.01	16.26	235.01	16.36	40.04	0.01	802.55
	Max	29.93	3.52	7317.94	410.31	287.22	1023.73	475.00	1681.25	1838.47	319.92	315.31	5165.92	23,631.49
	Mean	26.03	1.04	2922.24	76.70	120.28	312.78	124.67	574.60	630.72	154.36	130.14	1519.62	6534.56
	Medium	26.44	0.48	2529.56	0.01	103.66	192.29	28.88	485.71	520.09	138.39	121.07	909.93	4834.78
CA (*n* = 4)	Min	10.39	13.15	6633.73	252.94	228.97	516.80	305.56	1397.03	195.48	18.81	262.22	3465.35	3067.33
	Max	27.41	60.21	9476.04	1745.54	486.84	1093.86	1093.32	1750.00	1425.74	81.45	7922.52	5409.63	9108.60
	Mean	19.12	37.94	8152.84	1106.63	304.45	766.62	631.27	1620.80	632.91	42.58	4306.71	4093.09	5128.57
	Medium	19.33	39.20	8250.80	1214.01	251.00	727.91	563.11	1668.09	455.22	35.03	4521.05	3748.69	4169.18
UA (*n* = 2)	Min	0.56	-	483.84	26.83	1.28	0.89	0.01	0.01	850.00	147.67	227.54	0.01	33.72
	Max	1.35	-	762.33	144.88	2.34	1.32	0.01	96.54	2813.01	637.20	324.30	0.01	211.38
	Mean	0.96	-	623.09	85.86	1.81	1.11	0.01	48.28	1831.51	392.44	275.92	0.01	122.55
	Medium	0.96	-	623.09	85.86	1.81	1.11	0.01	48.28	1831.51	392.44	275.92	0.01	122.55
Mixed CO and CA (*n* = 3)	Min	25.44	0.04	1599.02	0.01	46.73	12.30	0.01	0.01	278.69	98.36	74.84	0.01	672.13
	Max	28.39	2.49	5864.34	297.81	248.71	616.80	451.20	992.03	859.48	187.25	245.08	4536.85	6743.03
	Mean	26.69	0.94	3251.99	99.28	117.06	252.69	150.42	462.49	491.94	143.13	163.71	2052.59	3153.64
	Medium	26.23	0.29	2292.62	0.01	55.74	128.98	0.06	395.42	337.65	143.79	171.22	1620.92	2045.75
Mixed CA and UA (*n* = 2)	Min	6.81	0.01	818.89	0.01	13.33	3.58	0.01	42.37	1690.68	288.14	143.64	0.01	420.00
	Max	16.75	0.10	897.03	61.89	44.49	16.47	0.01	52.22	2040.00	443.33	243.22	0.01	1597.46
	Mean	11.78	0.05	857.96	30.95	28.91	10.03	0.01	47.30	1865.34	365.74	193.43	0.01	1008.73
	Medium	11.78	0.05	857.96	30.95	28.91	10.03	0.01	47.30	1865.34	365.74	193.43	0.01	1008.73

Note: CO = calcium oxalate, CA = calcium apatite, UA = uric acid.

Digestion of kidney stones was performed by HF-HNO_3-$HClO_4$-HCl based on previous studies [12,20,21]. The 2 mL concentrated HF, 1 mL concentrated HNO_3, and 0.5 mL $HClO_4$ acids were applied to the weighed sample powder (around 30 mg) in the PFA beakers at 120 °C over 48 h. The strong oxidation properties of the mixed acid can dissolve the samples very well. After that, the solution was evaporated, and 1 mL concentrated HNO_3 and 3 mL concentrated HCl (aqua regia) were added into beaker at 120 °C over 24 h. The digested samples were measured of major and trace elements by Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES, Optima 5300DV, PerkinElmer, Waltham, MA, USA) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Elan DRC-e, Perkin Elmer, Waltham, MA, USA) in the Institute of Geographic Sciences and Natural Resources Research, Chinese Academy of Sciences [22–24]. Calcium (Ca), magnesium (Mg), sodium (Na), and potassium (K) were determined by ICP-OES, while strontium (Sr), zinc (Zn), copper (Cu), lithium (Li), titanium (Ti), selenium (Se), rubidium (Rb), barium (Ba), and lead (Pb) were measured by ICP-MS. The method's quality control was ensured through blanks, duplicates, and standard reference materials (Alfa 046318 and Alfa 036371), and the analysis precision was >±5%.

One-way ANOVA with the least significant difference test was conducted to determine the significance of the differences between the stone types. Relationships between elements were determined using the Pearson correlation coefficient. Principal component analysis (PCA) was used to determine distribution of data points and to describe the chemical composition of the kidney stones. Statistical analyses were conducted by the SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

3. Results and Discussion

Infrared spectroscopy showed the specific peak of each mineral (Figure S1), as follows briefly: five bands ranged from 3486 cm^{-1} to 3060 cm^{-1} and a high band from 1618 cm^{-1} to 1312 cm^{-1} for calcium oxalate, two high bands at 1465 cm^{-1} and 1028 cm^{-1} for apatite, and four high bands from 3600 cm^{-1} to 2600 cm^{-1} for uric acid [25]. The kidney stone types vary concerning composition and pathogenesis [26]. The stone type influences the elemental composition of kidney stones and their function [1]. Calcium oxalate is the most commonly occurring mineral phase in kidney stones, occurring at a frequency of roughly 70% to 75%, while the frequency of carbonate apatite and uric acid is 33% and 10%, respectively [27]. The average content of major and trace elements in different stone types was shown in Figure 1. CO is Ca salt with chemical forms (calcium oxalate monohydrate, $CaC_2O_4 \cdot H_2O$ and calcium oxalate dihydrate, $CaC_2O_4 \cdot 2H_2O$), as well as CA ($Ca_{10}(PO_4)_6CO_3 \cdot H_2O$). CO and CA represent inorganic components, while uric acid ($C_5H_4N_4O_3$) is organic. UA stones usually are radiographically transparent unless mixed with radiopaque Ca stones [1,28], which is the same as our results that Ca is the most abundant in kidney stones except for UA unless mixed with CO (Figure 1a). The fact that Ca is the major element is reasonable because most kidney stones are composed of calcium oxalate hydrates [14,15], Ca crystallization products from urine. The average content of Ca in CO (26.03%) was higher than that in CA (19.11%). However, the average content of magnesium (Mg) in CA (37.94 mg/g) is significantly higher than that in any other type (Figure 1b). The similar Ca content (26.69%) and Mg content in mixed CO and CA (Figure 1a,b) indicated that CO components dominated the mixed CO and CA type. As reported by a previous study [29], an explanation of CA enrichment by Mg is that struvite or newberyite is in apatite stones, and CA can absorb many chemical elements due to sparse properties. Apart from Ca, Mg is the most prevalent element in kidney stones, and is involved in a variety of biological activities. Mg functions as an inhibitor of the production of kidney stones, acting via absorption on the crystal surface and impeding new ion attachments, eventually preventing their aggregation [1,30]. As for trace elements, they are fundamental components of biological structures, and are required for many crucial bodily activities [31,32]. However, these metals may be hazardous in doses higher than required for biological functioning [13]. Additionally, trace elements impact the crystallization rate and the exterior shape of developing crystals [17]. As shown in Figure 1c,d, the average content of elements showed significant differences by the stone types. CA had significantly higher content in many elements than any other stone types except for Pb, Cu, and Se. These results agreed with a previous study that phosphate stones had a high Zn and Sr concentration more than calcium oxalate stones [33]. In kidney stones, strontium apatite made up 80% of the Sr, whereas strontium carbonate made up 20% [6]. In contrast, UA only had higher content in Cu and Se. Cu is an antioxidant present in the liver, kidneys, heart, and brain at the highest concentrations, as liver and kidney can be harmed under long-term Cu exposure [1]. Uric acid is synthesized similarly in the liver, adipose tissue, and muscle, and is mainly eliminated by the urinary system [34]; furthermore, uric acid is hypothesized for providing an antioxidant defense in humans [35]. Se may cause calcification of the kidneys and influences urolithiasis [36,37]. Therefore, the Cu and Se content probably implied the source of uric acid. CO had the highest Pb content compared to other stone types (Figure 1d). These results agreed with previous studies that inorganic stones had elevated Pb quantities while organic components such as UA were almost Pb-free [33,38]. Pb is a potentially toxic element, inducing renal damage regardless of low

or high concentration, and impedes waste product excretion out of the body [33,39]. Pb is closely related to environmental contamination [19]. In the comparison of Pb content from other regions (East Azerbaijan: 10.8 μg/g; Khouzestan: 108.5 μg/g; Fars: 12.1 μg/g) [12,13], our low average Pb content (6.5 μg/g) indicated that no Pb pollution occurred in this study. Kidney stone formation is closely related to age and gender [31]. In this study, the ratio of male to female is 2.75:1, which agreed with a previous study that kidney stones are two to three times more common in male than female [32]. There is little difference in the number of age distribution between 40–49 years, 50–59 years, and over 60 years, which is different from a previous report that the occurrence of kidney stones are mainly in those who are 40–49 years [40]. However, since there was a limited number of studied samples (n = 30), no significant relationship was found between chemical composition of kidney stones, age, and gender.

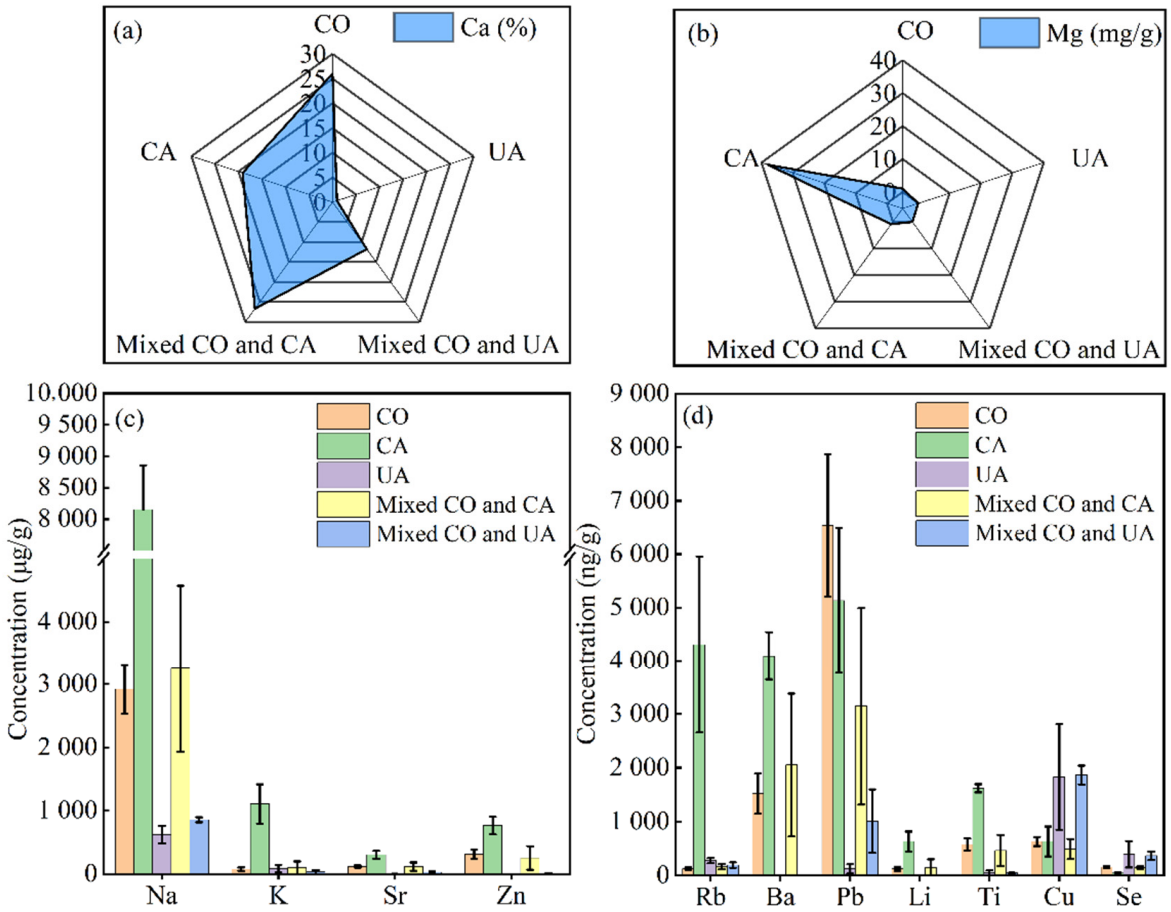

Figure 1. The content of elements in the kidney stones: (**a**) Ca content; (**b**) Mg content; (**c**) major element content (Na, K, Sr, and Zn), and (**d**) trace element content (Rb, Ba, Pb, Li, Ti, Cu, and Se).

The Pearson correlation was conducted to explore possible relationships and sources of analyzed elements in kidney stones (Figure 2a). Ca has good positive correlation with Mg (R = 0.60), Na (R = 0.64), Sr (R = 0.65), Zn (R = 0.70), Li (R = 0.64), Ti (R = 0.73), and Ba (R = 0.67), implying that there is a possible thermodynamically advantageous substitution process for these elements or a predisposition for their absorption by the oxalate crystal structure. When ion binding is considered, Mg^{2+} binds oxalate more easily than Ca^{2+} due to its smaller size, which allows it to occupy the binding sites, and reduce the rate of oxalate formation [41]. Riley also found Mg^{2+} would be trapped when approaching oxalate ions and the ability to compete for binding sites with Ca^{2+} was reduced, and therefore, the effect of Mg^{2+} was concentration-dependent [41]. Na substitutes Ca due to comparable ionic radius in minerals such as plagioclase ($NaAl_3S_{i3}O_8$-$CaAl_2Si_2O_8$) [42]. Sr

can create insoluble compounds with phosphates and oxalates, which can form kidney stones; furthermore, the human body handles Sr similarly to Ca, which facilitates Sr to replace Ca during biomineralization [6,43]. Similarly, both bivalent ions (Zn and Sr) have a substitution process of Ca due to comparable charge and radius [44]. Ca shows a poor correlation with K (R = 0.31) due to their distinct properties, which agrees with the previous report of their correlation (R = 0.19) [12]. Cu has been reported to have an influence on the growth of calcium oxalate at very low concentrations [1,33], which may cause the poor correlation between Cu and Ca (R = −0.38). The origin of trace elements is closely related to the regional water condition, meal, and living environment of patients [45–47]. As discussed above, Pb intake is affected by diet, geological environment, and pollution [12], which may result in a poor correlation (R = 0.44).

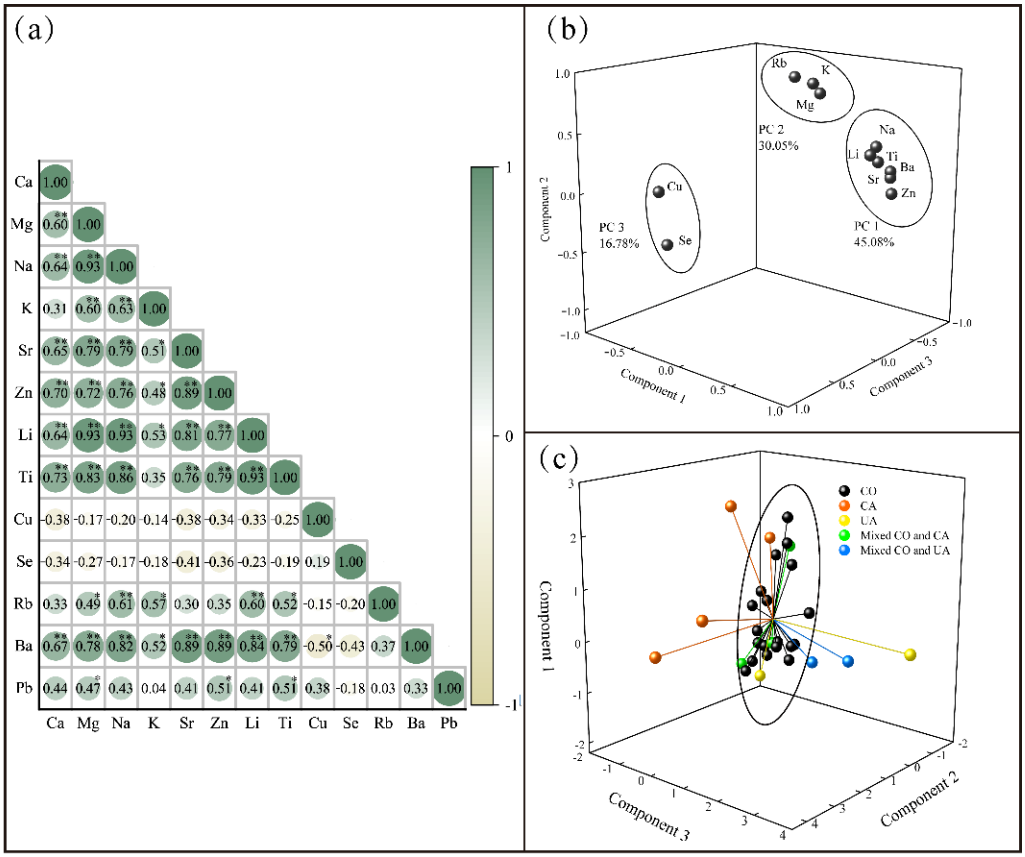

Figure 2. (**a**) correlation analysis in calcium oxalate stones; (**b**) principal component analysis of elements in kidney stones, and (**c**) scores of kidney stones in principal components. ** $p < 0.01$; * $p < 0.05$.

PCA analysis was used to identify correlations between data points and summarize the chemical content in the kidney stones. Before PCA analysis, data were normalized. The relationships between elements are displayed in Figure 2b. Three main principal components (PCs) were extracted with Kaiser–Meyer–Olkin index of 0.796 (>0.6) and $p < 0.05$, and the total variance was 91.91%. The first principle component (PC1) accounted for 45.08%, including a high positive load of Zn, Ba, Sr, Ti, Li, and Na. The second principle component (PC2) accounted for 30.05%, including a high positive load of Rb, Mg, and K. Furthermore, Cu and Se comprised the third principal component (PC3), which accounted for 16.78% of the total variance. The three PCs classified the elements and revealed a possible co-uptake or co-substitution process of these elements, to some extent, when forming kidney stones in the human body. Compared to our previous study [48], similarly, the element Na, K, and Mg, Cu still contributed to PC1, PC2, and PC3, respectively; however, Ba contributed to PC1 rather than PC2, which was probably attributed to its

high correlation with Na. Furthermore, in order to better show the discrepancy in kidney stone types than the previous study, we calculated the sample scores in three principal components in Figure 2c. The spatial distribution of stone types was significantly different in three principal components. Combined with the above element content analysis, the type of mixed CO and CA, and the type of CO had the same distribution behavior, indicating CO dominated the mixed type and they contributed to PC1. When the organic component (uric acid) was added, the spatial distribution tended to PC3. As for the type of CA, they contributed to PC2. The significantly different element distribution by stone types can be a good indicator for patients' intake of nutrients according to their disease. Stone formation is caused by dehydration (low fluid intake) [49]. Unhealthy life style such as high dietary intake of animal protein, sodium, sugars, and obesity are also major risk factors [50]. Therefore, exercise and a healthy diet are the keys to avoiding kidney stones.

4. Conclusions

This study reported that kidney stone types, including calcium oxalate, carbonate apatite, and uric acid, differ significantly in major and trace elements' content. Uric acid generally has a very low content of elements except for Cu and Se, which are probably from the liver. Carbonate apatite stones have a higher element content (such as Na, K, Sr, Zn, Rb, Ba, Li, and Ti) than calcium oxalate stones, especially enrichment of Mg. The significantly positive correlation between elements and Ca indicated that Ca is replaced or elements are precipitated with a large amount of calcium oxalates or phosphates during kidney stone formation. The PCA analysis classifies elements by their properties and stones types, indicating the influence on the enrichment of different elements by stone types. This study reports the preliminary distribution of major and trace elements in different stone types, which can be an essential reference for element intake, daily diet, and medicine of patients suffering from kidney stones.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/min12050512/s1, Table S1: Major and trace elements of all kidney stones. Figure S1: Infrared spectra of kidney stones as follows: (a) calcium oxalate; (b) carbonate apatite; (c) uric acid; (d) mixed calcium oxalate and carbonate apatite; (e) mixed calcium oxalate and uric acid.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Peking University Third Hospital (protocol code (2021) MSREC 475-1, 8 November 2021).

Informed Consent Statement: The informed consent exemption is included in the Ethics Review Approval Notice ((2021) MSREC 475-1).

Data Availability Statement: The data presented in this study are available in the Supplementary Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

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