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Coherent Scatter Computed Tomography for Core Composition Analysis of Intact Kidney Stones - Prospective Clinical Study

Cristian Dihel
The University of Western Ontario

Supervisor
Dr. Ian Cunningham
The University of Western Ontario

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

COHERENT SCATTER COMPUTED TOMOGRAPHY FOR CORE COMPOSITION ANALYSIS OF INTACT KIDNEY STONES–PROSPECTIVE CLINICAL EVALUATION

(Thesis format: Integrated Article)

by

Cristian Dihel

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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

THE UNIVERSITY OF WESTERN ONTARIO
School of Graduate and Postdoctoral Studies

CERTIFICATE OF EXAMINATION

Supervisor

_____
Dr. Ian Cunningham

Supervisory Committee

_____
Dr. Maria Drangova

_____
Dr. John Denstedt

Examiners

_____
Dr. Dan Goldman

_____
Dr. Jeff Chen

_____
Dr. Robert Stodilka

_____
Dr. James Warrington

The thesis by

Cristian Dihel

entitled:

Coherent scatter computed tomography for core composition analysis of intact kidney stones-prospective clinical evaluation

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Abstract

Urolithiasis is the presence of urinary calculi (urinary stones) at any level along the excretory system. Establishing accurate and complete mineral composition of the stones is one of the main factors in deciding the best steps for therapy and recurrence prevention.

Currently, infrared spectroscopy (IRS) and x-ray diffractometry (XRD) provide bulk composition results of urinary calculi in powdered form. Clinicians use the results to prescribe medical and dietary measures to restore the physiologic chemical balance of urine or rather alter it for the purpose of decreasing the crystallization rate of single or multiple minerals. As current methods have been shown reliable from a clinical perspective, they may also be, due to sampling bias, prone to missing the core components from the analysis.

This work shows that coherent scatter computed tomography (CSCT) is a composition-imaging, laboratory method able to provide both composition analysis of intact calculi and a distribution map of minerals within the stone, including its core and the surrounding layers. Aspects related to CSCT's measurement uncertainties, CSCT's analysis of kidney stones in both intact and pulverized forms and the summarized conclusions of a comparison study between CSCT and IRS are presented. With this new knowledge clinicians may choose to employ a core-targeted prevention plan in the management of urolithiasis to further decrease the recurrence rate in these patients.

Keywords

Coherent scatter, urolithiasis, core composition imaging, recurrence prevention.

Co-Authorship Statement

Chapter 2 has been submitted for publication to the “Radiology” Journal as “Coherent Scatter Computed Tomography (CSCT) as a laboratory image-based analysis of core composition in intact kidney stones-prospective clinical evaluation” by C. Dihel, J.D. Denstedt and I.A. Cunningham. I designed and performed the experiments using the existing CSCT device at Robarts Research Institute. I wrote the manuscript under the supervision of I.A. Cunningham and J.D. Denstedt.

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Chapter 1

1 Introduction

Urolithiasis is a serious health problem in humans and animals. Diagnosis can be straughtforward based on clinical symptoms, but in imaging techniques are often used for confirmation [1]. Procedures with various degrees of invasiveness are used for kidney stone removal. Despite advanced knowledge of both mineral and organic chemical constituents found in stone composition, and well established preventive measures for each constituent, prevalence and recurrence rates of urolithiasis are still on the rise [2].

Kidney stone recurrence ratesare very high, and part of a comprehensive program for medical management of the patients is to attempt to prevent future recurrences. Composition analysis after removal is one of the main considerations required for effective recurrence prevention [2]. Current analysis techniques, including infrared spectroscopy (IRS) and x-ray diffractometry (XRD) require pulverization of the stone before analysis, and since stones often consist of layers of different components, these methods are not able to specifically determine the composition at the core of the stone associated with the initial crystallization event. A method of analysis that provides structural information as well as composition may allow for identification of the core material and solve this problem. This thesis describes the results of a study that uses a novel analysis tool developed in our laboratory that generates two or three-dimensional images showing the distribution of component materials in an intact stone. These material “maps” show how the stone components are often structured into layers, and that

the core material, often a small fraction of the total stone mass, can be miss-identified by conventional methods.

This chapter describes urolithiasis with respect to its history, clinical symptoms, epidemiology, treatment and prevention. It also summarizes current composition-analysis techniques used in laboratories, as well as our new method, coherent-scatter computed tomography (CSCT), an image-based technique for analysis of urinary calculi in intact form.

1.1 Overview of urolithiasis

Kidney stone disease has been known to affect humans and animals for hundreds of years [3]. With people recognizing with ease the signs and symptoms of urolithiasis, came the struggle to find more efficient ways to treat and, even better, to prevent the occurrence and relapses of kidney stones.

While in 1500 BC the Ebes Papirus mentioned the “bread in a rotten condition” to treat bladder diseases and 1000 years later Hippocrates recognized the danger of bladder stones and initiated the analysis of urine by inspection and tasting [3], it was only in the past few centuries that more modern, thorough approaches to urolithiasis LEAD to the discovery of more beneficial diagnosis and therapy modalities of urinary calculi.

Although many urological treatments and techniques were developed as early ast the 16th century, it is remarkable that the first x ray of a kidney stone (in an abdominal film) was reported in 1896, the same year as the first reporting of the discovery of x rays by

Roentgen. Imaging kidney stones by x-rays has quickly developed as one of x-ray imaging applications [4]. The first retroperitoneal pneumatography in 1921, and the first intravenous urography in 1929 [3], were two other important milestones in the use of x rays for imaging kidney stones and their intimate anatomical structures.

The high social impact and economic burden of urolithiasis continues to drive the development of new solutions for treatment and prevention today.

1.2 Urolithiasis-epidemiology and clinical features

It has been determined that all categories of population are at various degrees of risk of developing urinary calculi [5]. Uncommon before the age of 20, kidney stone disease observes an increased rate of incidence with age and remains elevated until the age of 70, when rates tend to decrease [6]. There is a documented higher risk of developing kidney stones in men that in woman [6] [7] [5] [8]. Also, race, diet and lifestyle habits have an important influence on urolithiasis occurrence [5] [8]. It has been underlined by several studies that whites have the highest while blacks have the lowest prevalence rate for kidney stone disease. Hispanics and Asians have intermediate prevalence rates [5].

Seasonal variation, climate and geographical influences have been demonstrated by higher prevalence rates in populations living in dry and hot areas. In the United States, people living in southern states are prone to develop kidney stones more often than those living in northern states. This is likely due to inadequate hydration effects, and it has been estimated that by the year 2095 areas representing a high risk for developing kidney

stones will move further northward due to global warming and will comprise around 70% of the United States' population [9].

Various underlying disorders influence kidney stone formation and recurrence. For example, links have been demonstrated between cystinuria and cystine stones, between certain urinary tract infections and struvite stones, and between gout and uric acid stones.

Hyperparathyroidism, hyperthyroidism, renal anatomical anomalies are also associated with a high risk of kidney stone formation [6] [7] [5] [8] [9] [10] [2] [11] [12] [13], and must also be considered as part of the treatment and recurrence prevention strategies.

Most stones evolve undetected for long periods, often many years. In case of non-obstructive stones, haematuria is usually the first clinical feature that raises suspicion of the disease. Stones with diameter under 5 mm can easily start their passage through the uretero-pelvic junction and can generate obstructions and consequently renal colic (Figure 1). This starts often as a mild discomfort or vague pain and reaches a peak of severity in about 30-60 minutes [5] [7]. The pain is not influenced by position or movement; it is often associated with nausea and vomiting and cannot be relieved by non-narcotic pain killers [5]. When stone obstructs in lower excretory system main symptoms are bladder instability, dysuria and urinary frequency [5] [10] [12].

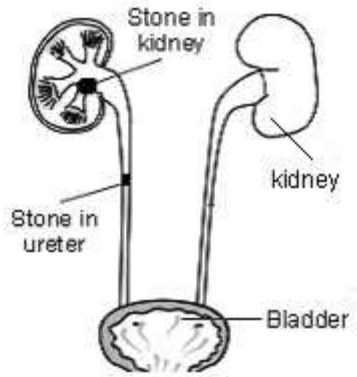

Figure 1.Excretory system schematic with potentially obstructive stones being present in the kidney and ureter.

These severe and debilitating symptoms emphasize the importance of conducting extensive research in order to discover new ways for more effective diagnosis, treatment and prevention of urolithiasis and its frequent recurrent episodes.

1.3 Urolithiasis-therapy

Comprehensive treatment of kidney stone disease must address acute episodes, stone removal and recurrence prevention. As in any acute scenario, the first thing to alleviate is the pain. A combination of anti-inflammatory and spasmolytic agents is usually attempted first. Narcotics may also be considered if the pain does not resolve. The intense, colicky pain explains the great social impact of urolithiasis as patients in some occupations, like airplane pilots [5] are not permitted to work even if they have asymptomatic stones. Notable also is that renal colic is so severe that it often requires the prescription of narcotic analgesics.

When the pain is under control, patient management continues with a decision for strategy of stone removal. Small stones that are less than approximately 5mm are often left in place and, based on location, may be eliminated spontaneously with no further intervention. For larger stones, or stones whose evolution is not expected to regress, as well as certain types of stones (staghorn or infectious stones), surgery is the elected option for removal. Larger stones that occupy part of, or all of, the renal pelvis must be removed to avoid potential renal functional complications.

Extracorporeal shockwave lithotripsy (ESWL) is a minimally invasive, outpatient procedure that crushes the stones in situ and the resulted fragments are expected to be eliminated afterwards with the urine flow. The procedure is relatively simple (Figure 2), but not without complications and has to be repeated when large fragments remain in place.

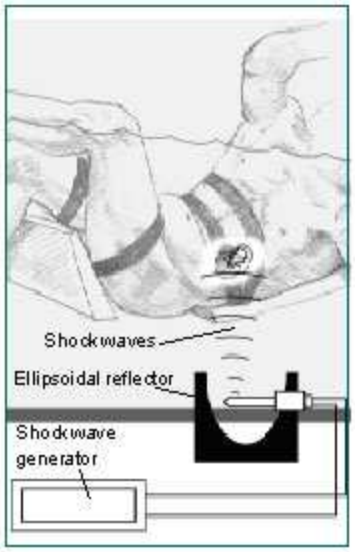

Figure 2. Extracorporeal shockwave litothripsy scematic diagram (http://www.healthxchange.com.sg/healthyliving/SexualHealth/Pages/Kidney-stones.aspx)

Endoscopic procedures (ureteroscopy, ureterorenoscopy) are outpatient procedures used quite often for stone removal, offering easy access to stones lodged in urethra, ureters or the vezico-ureteral junction (figure 3).

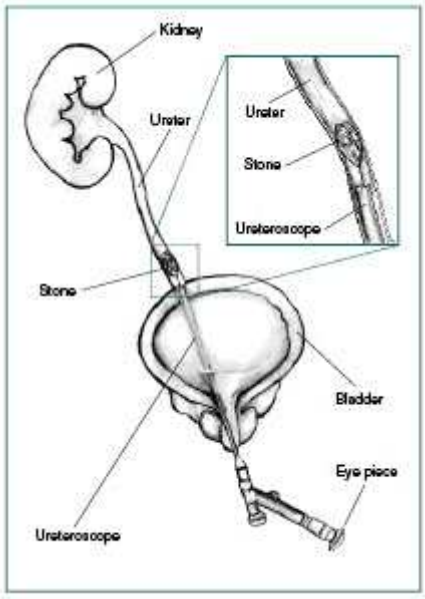

Figure 3. Ureteroscopy schematic diagram (http://www.healthxchange.com.sg/healthyliving/SexualHealth/Pages/Kidney-stones.aspx)

Percutaneous nephrolithotomy (PCNL) is an invasive intervention (figure 4) reserved for large calculi in the renal pelvis [5]. Classic, open surgery is being done in extremely rare cases.

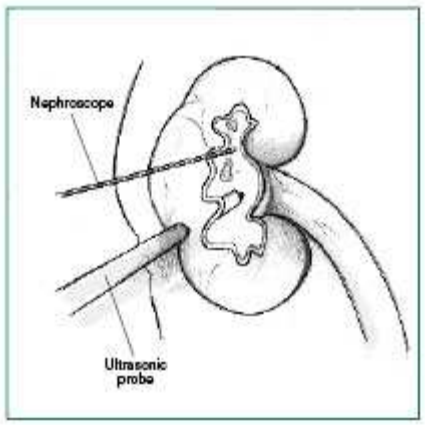

Figure 4. Percutaneous nephrolithotomy schematic diagram (http://www.healthxchange.com.sg/healthyliving/SexualHealth/Pages/Kidney-stones.aspx)

1.4 Urolithiasis-recurrence prevention

Once the stones are removed or expected to be removed by treating the causative element, the most important management step is deciding on a recurrence prevention plan. This may be dealt with by prescribing certain medications that address an already diagnosed underlying condition, such as in hyperparathyroidism or, more often, by recommending medication and diet based on bulk composition analyses. General preventive measures, such as increasing urinary volume [2] [5] [8] [9] [10] [11] [12] [13] to dilute the urine are always part of the recurrence prevention plan. This can be accomplished by increasing the daily fluid intake to 2.5 – 3.0 litres. Also, in case of calcium based stones, a decrease in calcium and oxalate intake and administration of potassium citrate and thiazide diuretics was proven to reduce the recurrence rate for calcareous stones. Ultimately, curative antibiotic treatment of persistent, chronic urinary tract infections with urea splitting bacteria can reduce the recurrence of infectious stones.

Diet low in methionine and sodium can decrease the frequency of cystine stones. Purine restriction, urinary pH elevation and administration of allopurinol can reduce hyperuricosuria [2] [8] [10] [11] [12] [13].

1.5 Kidney stone composition and metabolic associations

1.5.1 Common kidney stone minerals

All kidney stones contain 2-5% matrix (macromolecules and other cellular components) and 95-98% crystalline material. Most human stones are multicomponent containing more than one crystalline material [3] [14]. The most frequent minerals in kidney stone composition are calcium based, accounting for approximately 50-60% of all stones [3] [6] [7] [8] [10] [13]. The stones containing calcium salts can be either idiopathic or appear to be related to a pre-existing condition. Among non-calcium based stone components, the most frequent are struvite, uric acid and cystine.

Calcium oxalate monohydrate (COM), also called whewellite ($CaC_2O_4 \cdot H_2O$) is rarely found in nature but is the most frequent mineral in kidney stone composition. It presents as small, smooth, and yellow-green to brown crystals traditionally difficult to fragment [3] by shockwave lithotripsy.

Calcium oxalate dehydrate (COD), also called weddellite ($CaC_2O_4 \cdot 2H_2O$), was discovered in the 1930s in bottom sediments of the Weddell Sea in Antarctica. It is often found as sharp, yellow crystals deposited on the outer surface of a smooth COM stone. Occasionally, COD partially dehydrates to COM and they coexist in kidney stones, a fact explained by the epitaxial relations and similarities between the two crystals [15] [16].

Also, COD is generally associated with an active growing stone, while COM defines a more stabilized stone.

Calcium phosphate (CP) known as apatite, with its formula $Ca_{10}(PO_4,CO_3)_6(OH,CO_3)$, is a common mineral in nature and a very important component in bones and teeth. It appears as poorly crystallized in kidney stones and often forms the nucleus on which other minerals are deposited. The reported occurrence of apatite in kidney stones varies between 20-60% [8].

Calcium phosphate dehydrate (CPD) or brushite ($CaHPO_4 \cdot 2H_2O$) is encountered in kidney stones less often than apatite, with a 2-4% occurrence [8]. It is a soft, silky mineral, usually honey-brown, showing a fine radial fibrous structure.

Uric acid (UA), $C_5H_4N_4O_3$, appears in stones when the body breaks down purine nucleotides. It was the first kidney stone component to be described. It is present in about 10% of all kidney stones [14] and is associated with low pH values in urine. An increase of urinary pH above approximately 6.5 is shown to decrease UA stones recurrences.

Magnesium ammonium phosphate hexahydrate (MAP) or struvite ($MgNH_4PO_4 \cdot 6H_2O$) is associated with alkaline urine and is generally difficult to treat. It occurs with urinary infections caused by urea splitting organisms like *Proteus Sp.* or *Klebsiella Sp*. It tends to grow quickly and to occupy the structures of the renal pelvis, the reason that it often presents as staghorn calculi [3] [17].

Cystine (CYS) was isolated from a urinary calculus in 1810 and it was also the first known amino acid. Even though cystine, as a kidney stone component, is reported to

occur in only 0.5% of all cases, cystine stones are known to have the highest recurrence rate of all urinary stones, both with and without recurrence-prevention strategies [3].

1.5.2 Underlying conditions in urolithiasis

Extensive research has been directed towards identifying the conditions leading to stone formation and growth. Under normal circumstances, urine will not contain solid particles [3]. Calcium, as the main constituent of mineral compounds in kidney stones, is absorbed through the intestinal wall and deposited mainly in bones as apatite crystals. Calcium follows a continuous process of deposition and release from the bone matrix. At the renal level, calcium is filtered and reabsorbed in the normal urine formation process. Abnormalities, such as hyperparathyroidism, can lead to osteopenia with consequent pathologic fractures and nephrolithiasis due to an increase in urinary calcium filtration. Alternatively, any intestinal condition leading to an increased calcium and oxalates absorption can eventually translate into a urinary supersaturation in oxalates and calcium. Notable is that high urine concentrations in calcium and oxalates, and the resulting stone formation, has in most cases no apparent underlying cause and appears rather as idiopathic, related probably only to specific diet habits [7]. Citrates, as natural inhibitors in calcium crystallization, may also be present in low concentration in urine due to states related to loss of alkali in diarrhea or any other cause of metabolic acidosis [7].

In the case of calcium phosphate stones, the associated high urinary pH is regarded as a main risk factor. Interestingly, by an unknown mechanism [7], the urinary pH continues to rise as the concentration of calcium apatite in the formed stones is increasing, even under normal metabolic conditions (normal levels of bicarbonate in blood). Fluids,

thiazide diuretics may be attempted, but administration of potassium citrate can further increase urinary pH and thus must be carefully controlled.

Uric acid exists in equilibrium with urate as long as the urinary pH stays above 5.5. Hyperuricosuria, acidic urine pH or both are the main contributors in uric acid precipitation [3] [7]. Hyperuricosuria, occurring in gout or other conditions leading to hyperuricaemia, is not an essential factor in uric acid stone formation as these stones develop easily when urinary pH is lower than 5.5 with no uric acid metabolism abnormality.

Normally, infectious stones are not associated with metabolic abnormalities [8] but chronic recurrent urinary infections with Proteus Sp., some Klebsiella Sp. and even Pseudomonas Sp. lead to formation of large amounts of ammonium from urea and a resulting high urinary pH, thus helping in struvite crystallization. The high bicarbonate in urine also determines high carbonate concentrations and ideal conditions for calcium phosphate association with struvite in these stones [8]. In many cases struvite can be followed or replaced by other stone constituents [17] that make it a possible constituent to be found in the core as the start point in mixed stone formation.

Cystinuria, an autosomal recessive disease, is known to determine defects in renal and intestinal transport of amino acids like cystine, ornithine, lysine and arginine. Cystine is relatively insoluble which results in supersaturating of urine with cystine and stone formation. Medical management is usually not effective in cystine stones and most patients continue to redevelop stones and to undergo repetitive surgical procedures to have their calculi removed [3].

1.5.3 Current composition analysis techniques

Considered one of the most accurate composition analysis techniques [14], x-ray diffractometry (XRD) uses crushed stone samples for analysis and is based on comparison of standard diffraction patterns given by minerals most commonly found in kidney stones and expressed as interplanar d-spacing in Ångstroms with the diffraction patterns resulted from the actual stone sample. It is considered very accurate for determining the bulk mineral composition in kidney stones, but its limitations are the use of low energy x-rays (8 KeV) which are unable to pass through intact stones and therefore requires stone pulverization, inadequate sensitivity when a limited amount of sample is available [3], and high operation costs [14].

Infrared spectroscopy (IRS) also analyzes powdered samples of kidney stone and is based on the atomic vibration generated when infrared light interacts with the molecules in stone components [3]. The results are determined from predetermined material-specific energy bands in the absorption spectrum which are compared with standard absorption spectra from a set of calibration standards. These infrared patterns are reported as a function of wave number (wavelengths in units of cm^{-1}) corresponding to electronic vibrations in molecules. IRS is frequently used in kidney stone bulk composition analyses because it is quick, can deal with very small samples, and is inexpensive. Disadvantages are related to long preparation times (often manual stone pulverization) and low capacity of differentiating between uric acid and calcium phosphates, or between small concentrations of COD in COM or the reverse [14].

Microscopic examination of kidney stones (including polarized microscopy), although frequently used in urinary calculi analyses, is based on the assumption that all mineral

components have the same appearance all the time no matter the differences in mineral association or urine chemistry, which is not a sound assumption [3]. Stones are initially fragmented to reveal the internal structure, and then samples are taken from different parts of the stone for visual inspection and microscopic identification. It is inexpensive, allows for quick examinations, but requires high subjective experience and presents some difficulties in differentiating uric acid and purine derivatives from calcium phosphates [14].

Table 1 synthesizes some positive features and limitations of the three stone composition analysis techniques described above.

Analysis method	Advantages	Disadvantages
1. X-ray diffractometry (XRD)	-easy preparation -automatic measurements -quantitative analysis -possible exact component differentiation	-bulk composition, no core details -noncrystalline materials not detectable -high costs
2. Infrared spectroscopy (IRS)	-moderate costs -very quick examination -small sample examination possible -semiautomatic measurements -noncrystaline materials detectable	-bulk composition, no core details -time consuming preparation -some components difficult to differentiate
3. Polarized microscopy	-cost efficient -quick examination -small samples possible to examine	-high subjective experience necessary -some components difficult to differentiate -quantitative analysis difficult in mixtures

Table 1.Advantages and disadvantages of current kidney stone composition analysis techniques [14].

1.6 Urolithiasis-cost of care and social impact

Urinary stones are passed with no intervention in 90% of patients if their diameter is below 5mm. This spontaneous passage occurs in only 50% of cases if stone diameter is between 5-10 mm, while stones larger than 10 mm in diameter generally require surgical intervention [18]. Extracorporeal shockwave lithotripsy (ESWL) is considered the method of choice in treating simple renal and proximal ureteral calculi that fail to pass spontaneously. Ureteroscopy is preferred for distal ureteral stones, while percutaneous nephrolithotomy (PCNL) is reserved for complex renal calculi or when ESWL has failed or is contraindicated [19]. All of these therapeutic interventions are expensive with variable success rates depending on stone's size, location and composition, on patient's anatomical features and underlying conditions. One study has found ESWL to result in a lower success rate (70%) than PCNL (96%) with total costs of treatment of about $2,700 per case for ESWL and $4,100 for PCNL [6]. Annual rates of treatment have been on the rise, with a study in Quebec Canada showing a 59% increase in the number of patients undergoing at least one stone removal procedure over an 8 year period, with provincial total costs of $10.3 million in 1992 [20]. At the same time the annual cost of treatment in the United States was $1.83 billion in 1993 [18].

Medical management and secondary prevention of urinary stones was the main topic for both clinicians and researchers over the last years. Study results vary upon the cost and efficiency of medical management of urinary calculi. It is generally believed that medical management of the first stone would not be cost effective [11] [18]. However, secondary prevention through general and stone-specific dietary measures, as well as certain types of medication, have been shown to significantly reduce recurrence rates [8] [12]. Over a

period of five years, the total per-patient costs for urinary calculi medical management (non-surgical) including initial and follow-up visits, imaging procedures and drug expenses, vary from approximately $1,400 in Canada and Turkey, $4,000 in Italy and Sweden, and over $8,000 in the United States [18]. These costs are comparable to that of a single surgical procedure for urinary stones removal.

1.7 A New Imaging-Based Technology: Coherent scatter computed tomography (CSCT)

Coherent scatter of diagnostic x-rays was firstly described by G. Harding. He explained the theory of coherent scattering and emphasized the importance of x-ray coherent scattering, generally neglected for imaging purposes, and its fundamental importance for determining the material structure [21]. Coherent scatter computed tomography (CSCT) is a new imaging-based tool being developed in our laboratory that has potential for laboratory composition analyses of intact kidney stones [22] [23] [24] [25]. CSCT is based on a material-specific analysis of coherent scatter and associated diffraction of diagnostic x rays. The 70 kV x rays pass through a series of 3 x-y collimators to generate a pencil beam of about 1.5 mm^2. Between the second and third pair of collimators the beam passes a 0.30 g/cm^2 gadolinium (Z=64) filter for blur reduction. The stone sample is scanned meticulously, depending on the size and number of fragments, using 32 to 40 translations (covering the stone holder 2.5-cm diameter), 32 to 64 rotations and between 1 and 5 elevations. The number of elevations is given by the ratio between the height of the largest stone to be scanned and the height of the x-ray beam. A beam stop device is placed in front of an image intensifier, thus impeding the transmitted primary beam,

while the images of the resulting scattered rays at angles between approximately 0.5 and 10 degrees are acquired and converted into digital data. X-ray scatter produces a scatter pattern specific to each material due to diffraction of the x rays in the specimen. The scatter patterns from pure samples of the components found in urinary calculi are used to create a library of basis materials and used to identify the materials present in tomographic reconstructions of the stones and stone fragments. Seven of the most represented minerals in kidney stones were used as basis materials: whewellite (calcium oxalate monohydrate-COM), weddellite (calcium oxalate dehydrate-COD), apatite (calcium phosphate-CP), brushite (calcium phosphate dehydrate-CPD), uric acid (UA), struvite (magnesium ammonium phosphate-MAP) and cystine (CYS). The bases used in CSCT analysis are (except COD) pure, commercially available compounds (Sigma Aldrich Inc. and Fluka Chemie AG). Calcium oxalate dihydrate is represented by a powdered kidney stone reported by Infrared Spectroscopy (IRS) to contain at least 99% COD.

Each CSCT acquired scatter pattern is sectioned into concentric annuli due to its circularly symmetric nature. The signal in each ring is integrated and normalized by the solid angle corresponding to that particular ring, resulting in a cross-section curve. Composition analysis is performed by examining the coherent-scatter cross-sections in each pixel using a non-negative least squares (NNLS) regression. The measured cross-sections in each pixel is decomposed into its constituents, from which material specific maps are constructed. Images for each component are reconstructed using filtered back-projection reconstruction.

The composition analysis reports mineral concentrations both as grams/cm^3 and mass percentages relative to the entire stone. The reconstructed images identify the exact location of each mineral within the stone for each separate elevation. Figure 5 exemplifies clearly how CSCT identifies the location of different materials placed in different circular enclosures in a phantom made of polymethylmethacrylate (PMMA) containing pure minerals commonly found in the composition of kidney stones: A) CT image of the phantom; and B) to H) CSCT reconstructed images of COM, CP, CPD, PMMA, CYS, UA and MAP. Fields G) and H) also show that minerals, in this case UA and MAP, are exactly identified both as standalone materials and in mixture (circled enclosure). The two top enclosures on the left column contained air only and CSCT did not report a material in them.

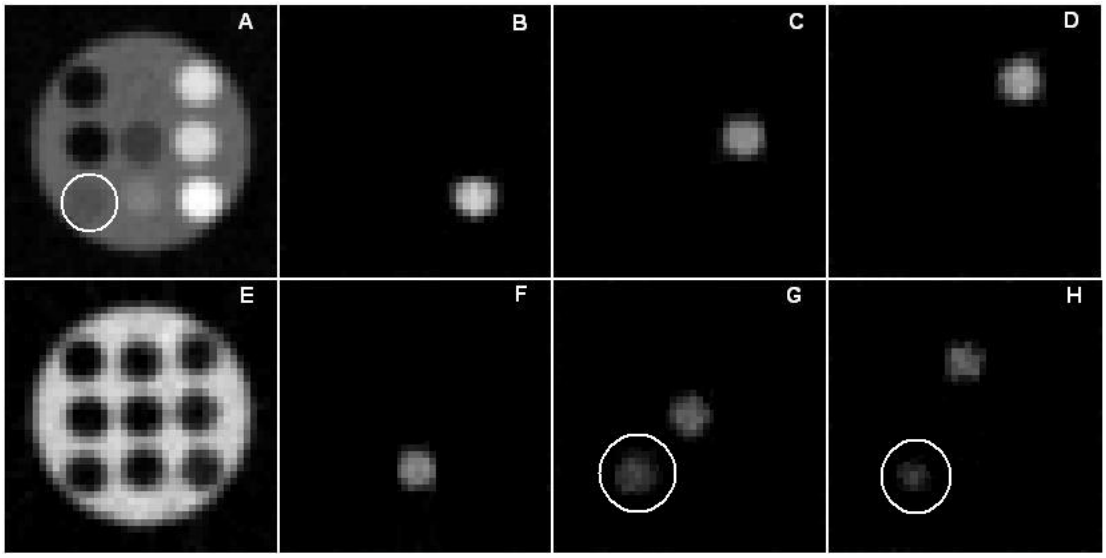

Figure 5.CSCT reconstructed images of a phantom containing several minerals in pure form or mixture.

The seven basis minerals used in CSCT material analysis are the most frequently found minerals in kidney stone composition determined by currently accepted techniques. It is a

real possibility that other minerals may also be present in kidney stones. We make the likely assumption that, since there is no basis scatter pattern for those materials in the CSCT calibration set, they will rather not be reported by CSCT than being miss-reported as one of the seven CSCT basis materials. Even if, as it will be shown later in the thesis, some basis scatter patterns present certain similarities with others, they always express differences as well. As shown in the above phantom experiment, CSCT succeeds in differentiating between minerals even in situations where their basis patterns are similar. It is unlikely that minerals not included in the calibration set of basis, would generate patterns identical with those from the CSCT basis minerals, and so they would not be reported by CSCT as one of the basis minerals.

1.8 Research Objectives

Strategies to reduce recurrence rates are an established component of patient management programs in most developed societies.

In the light of recent years advanced knowledge related to the multi-mineral composition of a large majority of the kidney stones, demonstrated associations or causative relations with major metabolic and genetic disorders [26] [27] [28] and recent research revealing that sustained and complex recurrence prevention programs may be effective, an imaging approach for non-destructive composition analysis of urinary calculi may contribute to a further reduction of kidney stone recurrence rate.

While well established, effective recurrence prevention programs are now employed in clinical settings, prolonging the time between episodes effective [29], studies show that overall recurrence rates remain at between 20% and 80% [2] [10] [11] [29]. One factor

that may be responsible for the continuing recurrences is that the laboratory methods of analysis described above provide bulk measures of mineral components and do not target the particular component at the core of the stone where nucleation was initiated. It is known that this core may be a small fraction of the total stone mass, and hence there is a concern that bulk measures do not have the sensitivity to report the core component. In addition, even if reported, these methods cannot make a distinction between a small but concentrated core of a particular component, or a distributed low concentration of the same component.

The goal of this research is to evaluate CSCT, the new imaging-based technology developed in our laboratory, for identifying where different material components may be distributed throughout an intact stone or large fragment. The implication is that if successful, a medical and dietary prophylaxis designed with both the specific component at the stone core as well as in outer layers might help reduce the recurrence rate of kidney stone disease.

The specific objectives are:

1) Conduct a clinical evaluation of CSCT on intact kidney stones and fragments from approximately 100 patients undergoing stone removal. Stone samples are examined (non-destructively) using CSCT and then submitted for conventional IRS analysis.

2) Compare bulk composition (mass fraction) of stone components reported by CSCT with IRS.

3) Determine composition of central core of stone as reported by CSCT, and determine whether IRS is reporting the same material in its bulk analysis.

These objectives are addressed in Chapter 2 of the thesis, consisting of a manuscript submitted to Radiology for publication.

Chapter 2

2 Prospective Clinical Study of Coherent-Scatter Computed Tomography for Laboratory Composition Analysis of Kidney Stones

2.1 Introduction

Prevalence of urinary calculi is between 5% and 12% depending on age, gender, climate and race [3] [6] [29], with an annual incidence rate of 0.5% in North America and Europe [5] and a lifetime recurrence rate with no prevention strategy varying from 50% to 80% [2] [5] [8] [10] [11] [29]. The number of recurrences is reduced in various degrees in the presence of certain medical and dietary prevention plans [29].

Most urinary calculi are calcium-based [8]. Stones made of struvite, cystine or uric acid are associated with certain medical conditions and occur less frequently, as shown in Table 2.

Crystal	Abbreviation	Frequency (%)	Association
Calcium oxalate monohydrate	COM	40-60	Metabolic abnormalities or idiopathic
Calcium oxalate dihydrate	COD	40-60	
Calcium phosphate	CP	20-60	
Calcium phosphate dihydrate	CPD	2-4	
Uric acid	UA	5-10	Hyperuricaemia, hyperuricosuria
Struvite	MAP	5-15	Urinary infection
Cystine	CYS	1-2.5	Cystinuria

Table 2.Common kidney stone components.

Many small stones are spontaneously eliminated but larger ones need fragmentation or removal by surgical interventions. A shift to less invasive, outpatient treatment modalities as a result of technological progress has been recorded in recent years, perhaps following an important increase in prevalence [29]. Recurrence prevention through diet and medication remains an important part of patient management and often very effective [13] [18].

Kidney stones are formed by various processes that include nucleation, aggregation and epitaxy, and often have a complex structure consisting of a core and one or more shells [16]. It is generally accepted that stone composition, and in particular the nucleating event, is an important indicator of stone etiology and a major factor in management of urolithiasis [1] [28]. However, stones are typically fragmented before removal and normal laboratory tests of composition, based on infrared spectroscopy (IRS) and x-ray diffractometry (XRD) involve pulverizing the stone [3]. For both of these reasons it is difficult to determine the specific composition of the initial core.

We are developing a new analysis tool called coherent scatter computed tomography (CSCT) that combines the strenghts of diffraction analyses with the benefits of tomographic imaging to determine distribution images of various mineral components in intact stones and stone fragments. The imaging capabilities of CSCT and preliminary stone analysis results have been previously reported [22] [23] [24] [25].

2.2 Objectives

The main objective of this work is to evaluate CSCT as a laboratory technique for structural and compositional analysis of intact kidney stones in a clinical study and to compare the results with IRS. Laboratory IRS has been shown to correctly identify minerals in the samples it has to work with [3] [28], and therefore we hypothesize that CSCT provides composition analysis results equivalent to IRS for identifying the most prevalent component in each sample while also revealing structural details and identification of the central core component.

Our goal is to evaluate the potential of CSCT as a method for stone analysis, and to highlight the importance of adopting an imaging-based approach for material analysis laboratory tests.

2.3 Material and methods

2.3.1 CSCT analysis

The CSCT system was design and constructed in our laboratory using a conventional x-ray tube and image detector [22] [23] [24] [25]. Scans use 70 kV x-rays, collimated to an approximately 1.25-mm square beam and passed through a gadolinium filter to reduce the energy spread of photons in the beam. A total of either 32 or 64 projections (depending on specimen size) were obtained covering an angular range of 180 degrees using first-generation CT geometry. Each projection consisted of 40 projection measurements at 0.63-mm center-to-center spacing, resulting in reconstructed images with 0.63-mm pixels, a 25-mm field of view, and 1.5-mm slice thickness.

The beam passes through intact calculi securely mounted on a stage that allows multiple elevations, translations and rotations. The emergent low-angle (0.5 to 10 degrees) scattered x-rays generate material-specific scatter patterns captured using an image intensifier and CCD (charge-coupled device) camera (Figure 6).

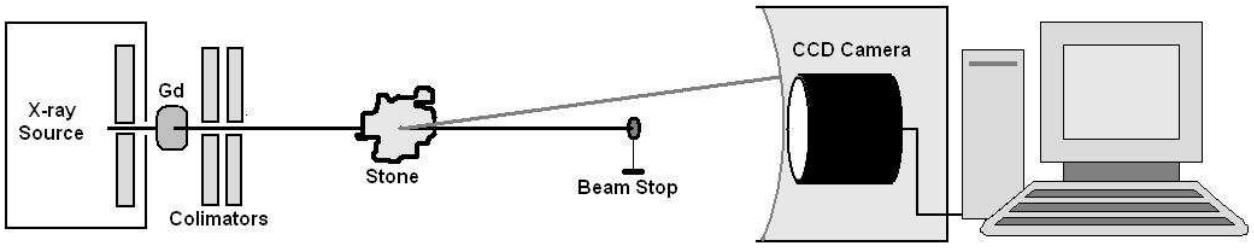

Figure 6. Schematic diagram of CSCT device. The scattered x-rays at angles between 0.5 and 10 degrees are collected and further analyzed for computed image reconstruction.

A material analysis of each pattern is performed by comparison with a set of scatter patterns generated by pure samples of minerals listed in Table 1. These are symmetric patterns with clear, well defined rings of various scatter intensities (Figure 7).

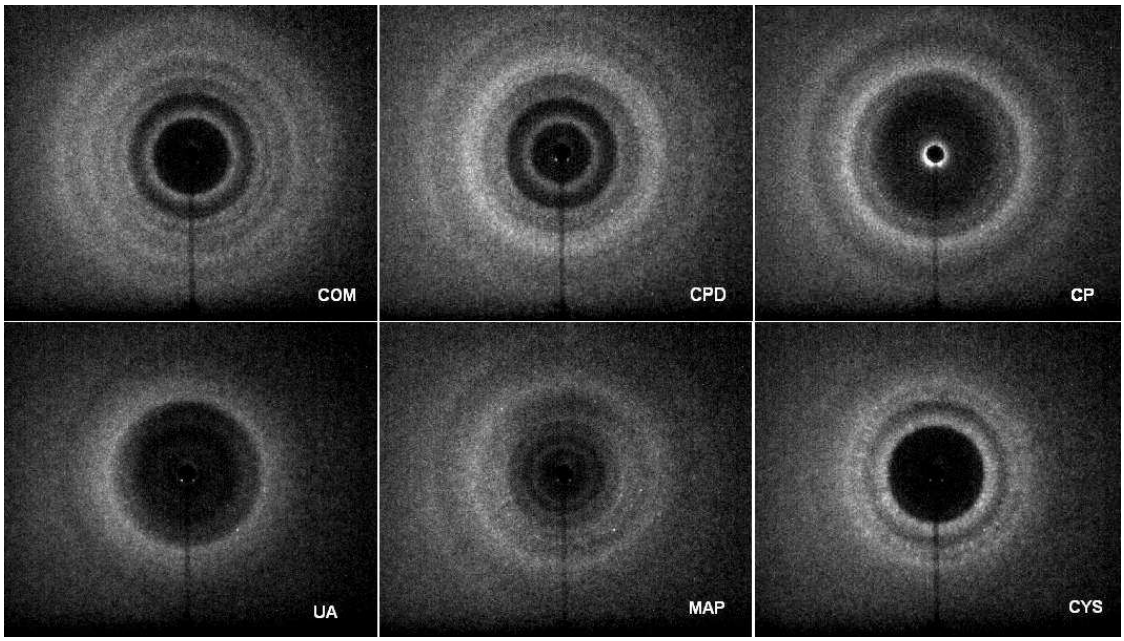

Figure 7.Example of basis scatter patterns of common kidney stone minerals.

Unlike other materials available in commercial form, a pulverized kidney stone identified by IRS as at least 99% COD was used to generate the specific scatter pattern for this mineral. In addition, COD generates a polycrystalline diffraction pattern containing multiple bright spots as observed in Figure 8 (left). The COD powder diffraction pattern was estimated by rotating the sample continuously during data acquisition, producing the pattern shown in Figure 8 (right).

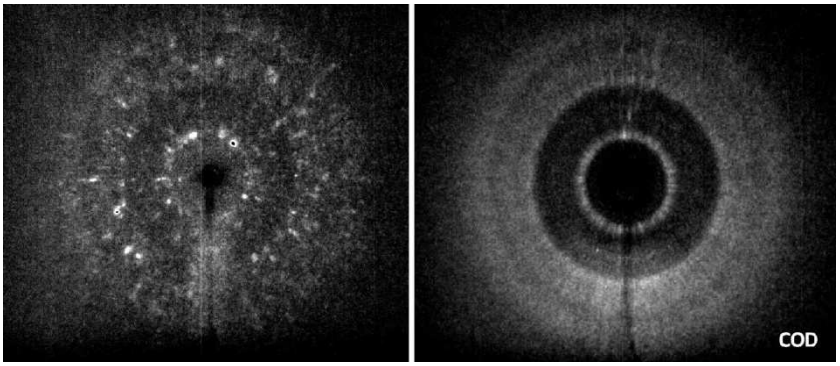

Figure 8. COD-static, polycrystalline scatter pattern with bright spots and poorly expressed diffraction rings (left), and COD-rotated, powder scatter pattern with uniform, well defined scatter rings (right).

The mass of each component material was determined for a range of positions and angles and used to reconstruct tomographic images of the distribution of each component in slices at multiple levels through the stone. The physical and mathematical approach of CSCT was previously described by Davidson et al [25]. While CSCT analysis provides the concentration of each component in g/cm^3, these were converted to mass percentages of the entire stone in order to compare them with IRS.

2.3.2 Measurement errors and uncertainties in CSCT analysis

The diffraction-pattern peaks produced by CSCT are broader than XRD due to the use of a diagnostic x-ray spectrum and may partially overlap. This problem is similar to that encountered by IRS [31], and we use a similar method of fitting the measured patterns to a set of calibration standards.

Five repeated scans were performed on capsules containing pure samples of each basis material in PMMA containers to assess the analysis precision. Each scan generated a set

of material-specific images that were analyzed for composition using the whole set of seven basis stone scatter patterns plus PMMA. The results were used to generate a response matrix describing the tendency for one material to be miss-identified as a different material. The response matrix was used to apply a correction for the miss-identification, although this correction affects only a couple of material combinations as described in the results section, and the correction was never more than 13%.

This experiment is limited to the situations in which the measured component is highly represented in the stone composition, with any of the other measured materials being present in very low proportions. For a thorough results correction in combinations of various proportions of materials in a kidney stone, a much larger experiment is needed. In the design of such an experiment all possible combinations of two or more components must be taken into consideration.

The precision of each measurement is determined primarily by the propagation of x-ray quantum statistics through image reconstruction and material analyses. Since the number of x-ray quanta in each pattern is proportional to the mass of the scattering sample, we make the likely assumption that the statistical variance in each measurement is proportional to the mass of the scattering material. For example, if repeated (independent) CSCT measurements of the mass of material j, m_j, have a variance $\sigma_{m_j}^2$, then we are assuming that the normalized variance, $\left[\frac{\sigma_{m_j}^2}{m_j}\right]$, is independent of m_j and can be measured and used as a known quantity to estimate the uncertainty in any subsequent measurement. That is,

$$\sigma_{m_j}^2 = \left[\frac{\sigma_{m_j}^2}{m_j}\right] \times m_j. \quad (1)$$

For a specimen with multiple components, we make the assumption that the addition of cross terms results in an approximate estimate of the uncertainty, giving

$$\sigma_{m_j}^2 = \sum_i \left[\frac{\left|\sigma_{m_{ji}}\right|}{m_i}\right] m_i \quad (2)$$

summed over all materials *i* in the material analysis, and where the quantities in square brackets, called the normalized material cross-covariance matrix, are measured and tabulated for the particular test conditions. Terms in the normalized cross-covariance matrix describe random mean-square fluctuations in the computation of material *j* for a measurement on physical material *i*, averaged over *k* repeated scans. Thus, each term is defined by:

$$\frac{\sigma_{m_{ji}}}{m_i} = \frac{1}{k} \times \sum_k^1 \left(m_{j_k} - \langle m_j \rangle\right)\left(m_{i_k} - \langle m_i \rangle\right) \quad (3)$$

2.3.3 Effect of stone pulverization on material analysis

Unlike IRS, CSCT uses intact kidney stones or fragments. To observe whether pulverization influences analysis results, a set of stones were scanned by CSCT in both intact and pulverized forms. Following the CSCT scan in intact form, each stone was crushed to a fine powder using a laboratory mortar and pestle for 5 minutes, then encapsulated in standard, pharmaceutical gelatin capsules for the second scan. A baseline

scan of an empty capsule was subtracted from the analysis results. The x-ray energy and number of angular projections and elevations were identical for each scan.

2.3.4 Comparison of CSCT and IRS for bulk composition analyses

A prospective clinical evaluation of CSCT was initiated in the Imaging Research Laboratories of the Robarts Research Institute with the Department of Urology at St. Joseph's Health Center. It was performed over a four year period and included 119 patients diagnosed with urolithiasis. All ethics approvals were obtained as necessary and patients signed a written informed consent. Stones collected through uretheroscopy or percutaneous nephrolithotomy were scanned and analyzed by CSCT, then sent to an external laboratory for IRS. The CSCT and IRS results were evaluated in terms of agreement for primary mineral component detected by the two methods and their ability to identify and determine the proportion of the core mineral.

2.4 Results

2.4.1 CSCT material analysis

Figure 9 shows the scatter patterns for the minerals described in Table 2. These basis patterns were used in the CSCT material analysis to calculate the mineral concentration in each projection measurement, and filtered back-projection methods were used to reconstruct mineral-specific images of each component.

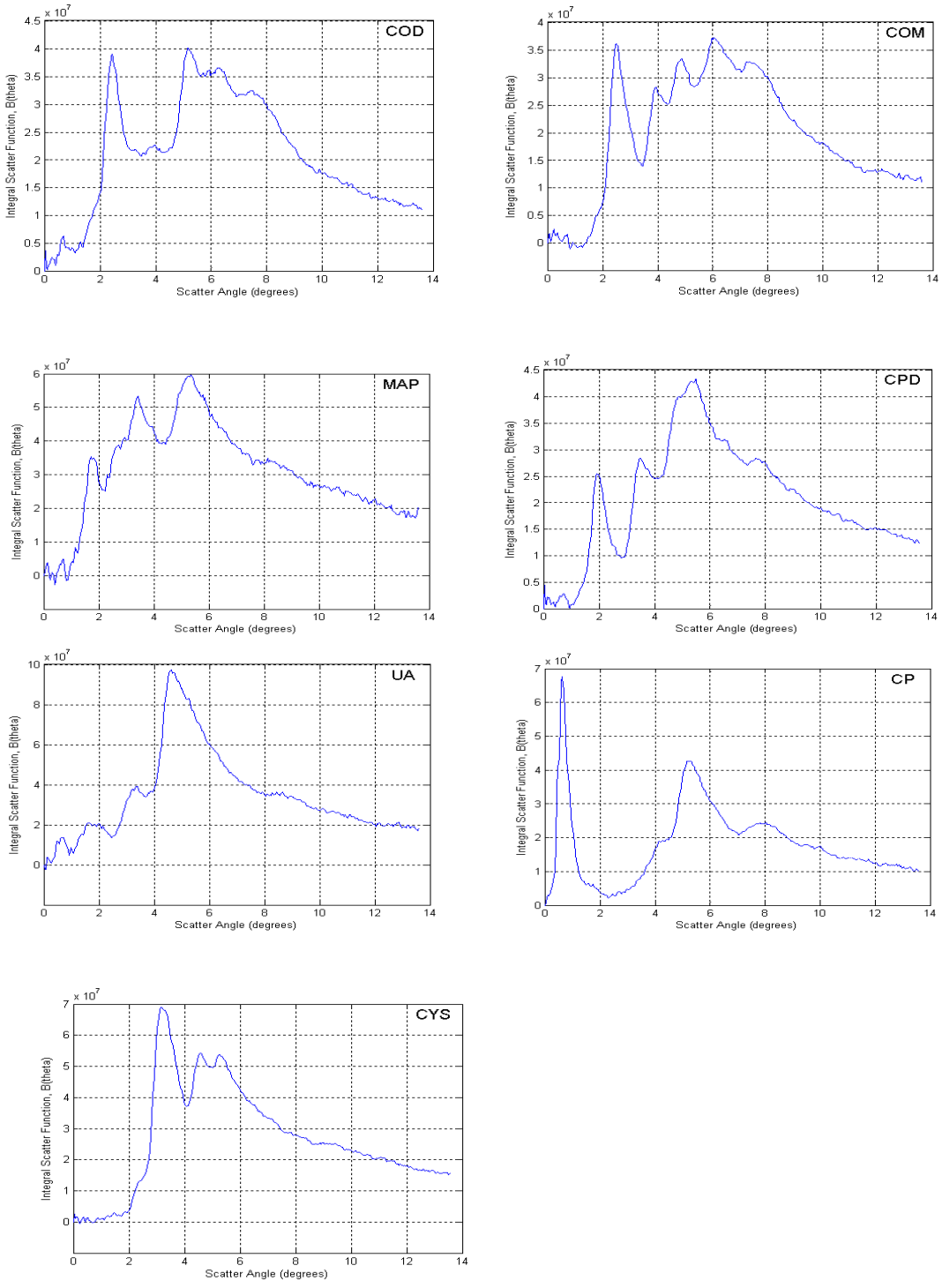

Figure 9. Scatter patterns of common kidney stone minerals. Each pattern consists of peaks superimposed on a background continuum. Similarities are observed in some peaks between patterns generated by MAP and CPD and by COD and COM. UA, CP and CYS show clearer distinction in their patterns.

Figure 10 shows the material-analysis result for a typical specimen consisting of one intact and one fragmented kidney stone. In these images, brightness corresponds to mass concentration (g/cm^3) of the two identified components (COD and COM) at each pixel location in one tomographic slice. Several slices were acquired to cover the entire volume of the specimen. The total mass of each component is reported in grams and converted to mass percentage of the entire stone. In this particular example, CSCT reported 80% COM and 20% COD while IRS reported the same sample as 90% COM and 10% COD. These two results are most likely within experimental error, but the IRS result misses the fact that the intact stone (left) clearly has a small COD core while all of the COM is in an outer layer. The other stone, fragmented into three pieces, likely has a similar composition as one fragment in particular (lower) shows a distinct central region of COD. Thus, rather than assuming the COD is a minor component in the analysis, the CSCT result clearly indicates that any prevention strategy should specifically target COD. In this case that would not likely impact on patient management.

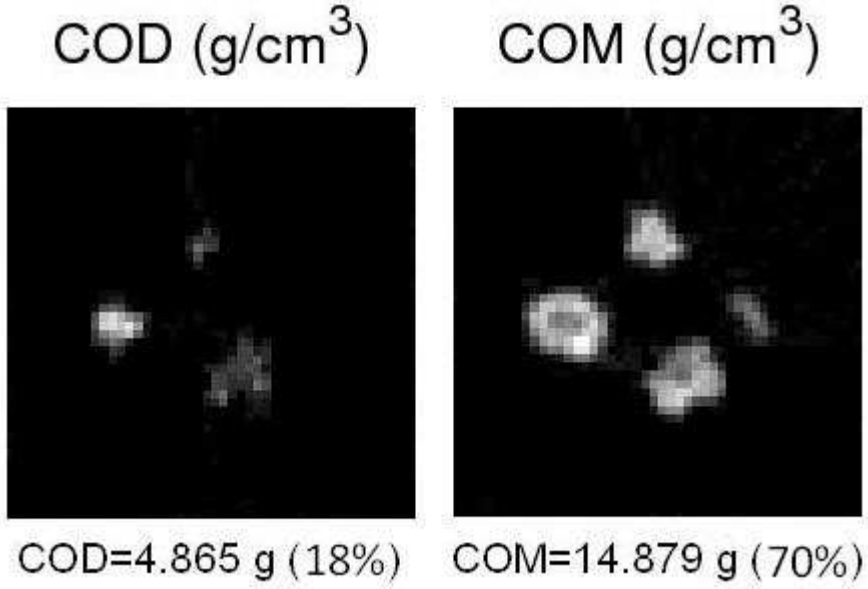

Figure 10. Example of CSCT analysis and mineral-specific image reconstruction showing an intact stone (left side of each image) and three stone fragments from the same patient.

2.4.2 Measurement errors and uncertainties in CSCT analysis

The composition analysis results for each basis material are summarized in Table 3. Each row describes the total mass of each reported material from the analysis of a pure specimen, normalized to 100% on the diagonal members. Thus, for example, the pure 182 g COD sample was reported as 182 g COD plus a miss-identification of 24 g (13% of 182 g) of COM. The pure COM specimen was reported as COM plus very small concentrations of other materials.

This data shows that COM, CP, CPD and CYS are all reported accurately with only very minor possible miss-identifications (<4%) of other materials. COD results in an additional 13% COM and 5% MAP. UA results in an additional 8% CYS and MAP

results in an additional 11% CPD and 8% CYS. These miss-identifications are reduced to less than 1% after correction by the response matrix.

		Reported materials (% g/cm^3)						
		COD	COM	CP	CPD	UA	MAP	CYS
Physical sample	COD, 182 g	100	13	2	2	0	5	3
	COM, 492 g	2	100	2	0	1	1	2
	CP, 302 g	0	0	100	0	1	0	1
	CPD, 477 g	1	0	2	100	2	2	1
	UA, 289 g	0	1	2	2	100	3	8
	MAP, 152 g	0	0	2	11	4	100	8
	CYS, 543 g	0	1	0	2	4	2	100

Table 3. The response matrix shows the reported proportions of materials (rows) for each each pure physical sample being analyzed (colums), averaged over five repeated CSCT scans. Each row is normalized by the diagonal element. For example, the top row indicates that a pure, 100 g COD is reported to consist of 100 g of COD plus 13 g of COM, 2 g of CP, 2 g of CPD, 5 g of MAP and 3 g of CYS.

The normalized cross-covariance matrix is shown in Table 4. For illustration, the statistical variance in a measurement of COD in a sample consisting of 200 g COD plus 50 g COM, using Eq. (2), is estimated as

$$\sigma_{COD}^2 = [1.53] \times 200 + [0.18] \times 50 = 315$$

corresponding to an RMS uncertainty in the COD measurement of 18 g (9%).

		Reported materials (% g/cm^3)						
		COD	COM	CP	CPD	UA	MAP	CYS
	COD	1.53	-1.03	-0.24	0.44	-0.03	0.40	0.12
	COM	-0.18	0.42	-0.15	-0.05	0.13	-0.03	0.11
Physical	CP	0.00	0.00	0.10	0.00	-0.01	0.00	0.00
material	CPD	-0.49	0.02	-0.20	0.98	0.05	-0.34	0.12
	UA	0.02	-0.05	0.08	0.07	0.13	-0.15	-0.19
	MAP	0.11	0.15	0.19	-4.10	0.96	8.40	-0.74
	CYS	0.08	0.03	0.03	0.09	-0.52	-0.05	0.69

Table 4. The cross-covariance matrix shows the statistical variance and cross covariance terms between reported materials (rows) for pure physical samples (columns), normalized by the concentration (g/cm^3) of the pure sample.

It should be noted that some cross terms are negative. For example, COD and COM are negatively correlated which means that in any one individual analysis, an increase in a reported COD amount is correlated with a decrease in the COM amount. This is a consequence of the two scatter patterns being similar. Patterns that differ greatly, such as CP and CYS, have a very small cross term.

2.4.3 Effect of stone pulverization on material analysis

The composition analysis results obtained from a set of kidney stones scanned in both intact and pulverized form were compared for agreement using Bland-Altman plots [32] [33].

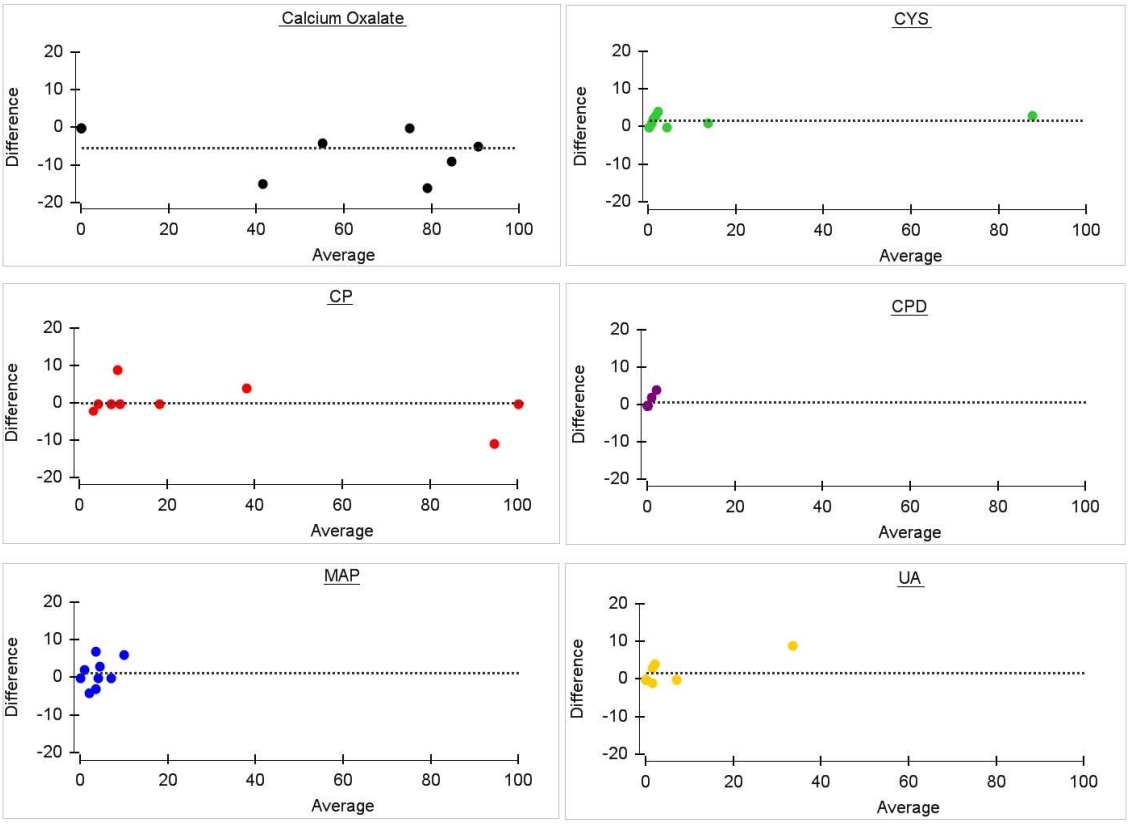

Figure 11. Bland-Altman plots suggest a strong agreement between CSCT analysis results of kidney stones in intact and powdered form. The mean difference is shown as dotted line. Both COM and COD were combined in the calcium oxalate results. The vertical axes show the difference between CSCT intact and CSCT powdered, while the horizontal axes represent the average between the two sets of results. MAP and CPD were not well represented due to a small sample size.

As shown in Figure 11, good agreement between the two sets of results was observed, all differences being less than 15% and most less than 5% of the mean, independent of their low or high proportion in the stone. Similar agreement was observed with the IRS results. It was therefore concluded that crushing the stones to fine powder had, by itself, no

influence over CSCT analysis results, but the draw-back for stone pulverization is the loss of all structural details available with CSCT scanning intact calculi (Figure 12).

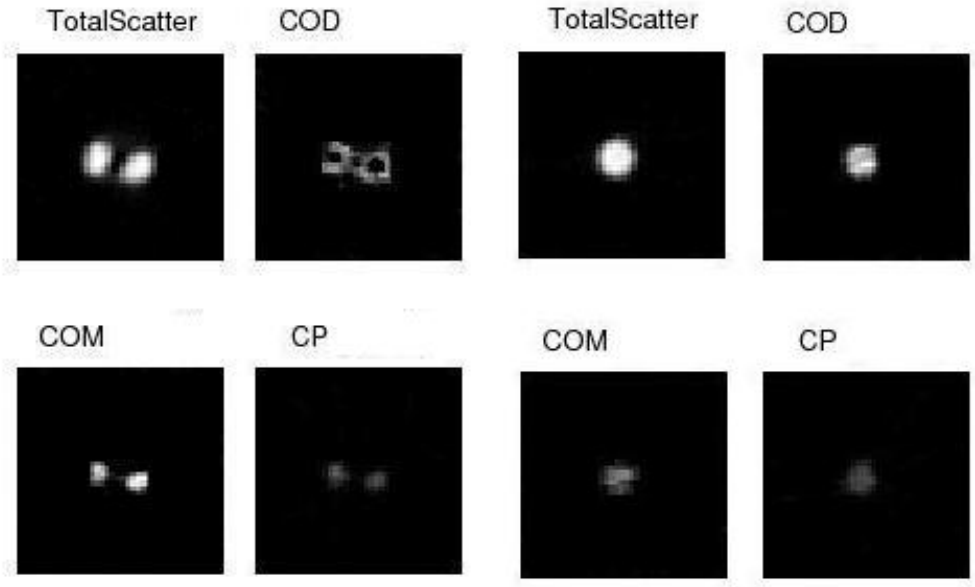

Figure 12. Kidney stones scanned by CSCT in intact form (left) with obvious CP+COM core surrounded by COD. Same stones scanned in powdered form (right) show same materials but also the loss of structural details.

2.4.4 Comparison of CSCT and IRS for bulk composition analysis

From a total of 119 patients, 34 either withdrew from the study, had no stone at the time of surgery, or their stone fragments were too small (<1 mm) to be scanned by CSCT. IRS has reported most stones as having one or two components. At the same time CSCT reported one, two and sometimes three minerals in stones. The analysis results reported by CSCT were corrected using the response matrix. Calcium oxalate based minerals (COD and COM) were considered as one group having, from a clinical point of view, identical strategies of recurrence prevention, unlike MAP, UA, CYS, CP and CPD that

generally have different recurrence prevention strategies. We used the terms of primary and secondary mineral to define the two minerals with the highest proportions reported in the composition analysis. In this respect, in 74 of 85 patients (87%) IRS and CSCT both reported the same primary materials. In 28 patients (33%) the primary and secondary minerals found by both methods were identical. In 3 patients, IRS and CSCT found different minerals to be the primary and secondary components in the stone composition. It is possible these differences may be related to sampling issues associated with stone pulverization and preparation preceding IRS.

CSCT image reconstruction found only a small number of stones to not express a classic "core & shell" structure, but rather a uniform geometry. On the other hand, IRS reported more than half the stones as containing only one mineral. As a result, in 35 patients (41%) CSCT reported a core material that was not found by IRS. In terms of core imaging and core composition CSCT was able to reveal the internal structure of intact kidney stones whether a distinct core existed or the stones were made of uniform mineral mixtures (Figure 13).

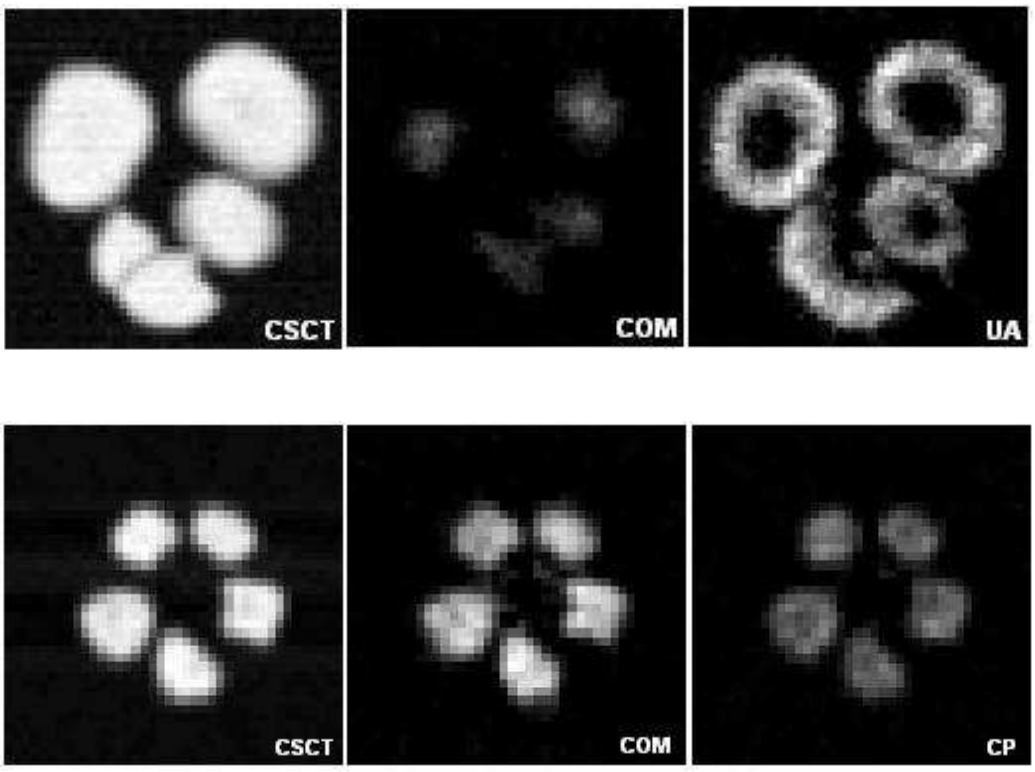

Figure 13. Examples of CSCT reconstructed images: stones with clear "core and shell" structure (above) and stones with more uniform, homogenous structure and no evident core (bellow).

2.5 Discussion

As a laboratory based, imaging technique, CSCT is a novel method of imaging the structure and determining the mineral composition at the core of intact kidney stones. If, as is generally accepted, a core-targeted recurrence prevention approach will be employed for recurrence reduction in stone formers, CSCT has the potential to become an important tool of choice in composition analysis of urinary calculi. In 52 patients (61%), the addition of supplementary measures in their recurrence prevention strategy may have

had an impact on their recurrences, since various amounts of MAP, UA, CYS and even calcium based minerals have been detected by CSCT and not reported by IRS.

The good agreement recorded between CSCT intact versus CSCT powdered on stone composition analysis shows that the analysis of intact kidney stones is possible and reliable. Pulverization, necessary for conventional IRS and XRD analysis methods, does not change analysis results but destroys the stone's geometry and the internal structure hence losing important information on core composition and limiting recurrence prevention to target only bulk composition results.

Despite scatter pattern similarities between COD and COM, CSCT demonstrates the ability to differentiate between them in the analysis, although from a clinical perspective, this differentiation is less important due to identical prevention protocols for calcium oxalate stones and the natural tendency of COD to transform into the more stable COM [34].

As expected, most stones in this study were calcium based with various associations between calcium oxalates and calcium phosphates. Many cystine stones were found to be uniform and not associated with other minerals. Common associations between all forms of calcium based minerals were found. Interestingly, MAP was detected in a number of stones as a secondary mineral and mostly as a core component. Even if MAP is known to occur in urinary infections related to urea splitting organisms such as *Proteus Sp*., it was shown before that all urinary stone constituents could join MAP in kidney stones [17]. We found 10 patients (12%) in which MAP was associated with UA, mostly with MAP as a core component. One form of uric acid, ammonium acid urate, has been previously

reported to appear in association with MAP or in the context of urinary infections and an alkaline pH [17]. It remains to be established whether urinary infections may trigger the nucleation process with MAP crystallization and growth followed by the deposition of other minerals on the already form nucleus. IRS missed the core mineral detected by CSCT in 35 patients (42%), which raises the question of whether these patients are missing the opportunity to have a core-targeted prevention plan to follow.

Undoubtedly, medical and dietary recurrence prevention measures have proven their efficacy [29]. As stated before, general prevention measures such as an increase in the use of thiazide diuretics and urine alkalinisation with potassium citrate can be very effective in many cases. In this context, the possibility of further recurrence reduction using a core targeted approach emphasizes the real value of using CSCT as an imaging based composition analysis technique.

Chapter 3

3 Conclusions and future work

3.1 Conclusions

3.1.1 CSCT reconstructed images for individualized stone characterization

Coherent scatter computed tomography analysis provides structural information of stone core and its surrounding layers not reported by IRS. The analysis of intact urinary calculi gives insight as to the arrangement of various mineral components within the stone, their intimate associations, offering at the same time the opportunity for interpretation of different pre-existing or co-existing metabolic conditions in stone formers.

Both CSCT and IRS reported the same primary material (most prevalent) in 74 patients (87%). This gives confidence that both CSCT and IRS are capable technologies. The core component found by CSCT was missed by IRS in 41% of cases. At the same time, when detected, the core mineral is reported by IRS only as part of the bulk composition analysis with no reference to its location within the stone.

Structural details like “core and shell” stone structure are undoubtedly useful in planning a recurrence prevention strategy that targets the core mineral(s). Moreover, this detailed information can also be valuable in deciding on treatment modality on repetitive stone formers, acknowledging that different minerals present different degrees of hardness and so different response to lithotripsy. In this regard, the development of data bases with

CSCT images of previous stones in highly recurrent patients may be helpful not only for comparison and research purposes, but also for rapid access and clinical decision making when these patients come to the clinic with relapses.

3.1.2 CSCT an alternative to classic analysis techniques

The agreement between CSCT and IRS on the main stone components demonstrates that both methods are technically accurate for composition analysis. The difference comes from IRS using one or several powdered samples from a stone, which can lead to sampling errors. When a surface sample is collected this may contain only limited amounts of core material depending on the size of the sample and the size of the core.

In our study, CSCT has shown that kidney stones may often contain two or more components. They are following a classic “core and shell” structure with a core variable in size surrounded by layers of different minerals. Due to the IRS sampling issues mentioned before, not only the core material but also other stone components may be under-reported by IRS. As a result, by compensation, IRS reports higher proportions of the materials detected, which may lead to the belief that the analyzed stone has a uniform, single-mineral composition. In reality the lesser represented minerals may be of great importance in understanding the process of stone formation and, in many cases these minerals could explain why the recurrences in some patients occur more often than in others.

In 61% of the study patients, CSCT reported the presence of a mineral not reported by IRS. In most cases the missed mineral was the core component, while in other patients

the missed mineral was part of the structures surrounding the core. What is possibly more important is that these components were from different classes of minerals with respect to recurrence prevention measures and thus these patients could have had the option of a more complex recurrence prevention strategy.

It is also true that some disorders, such as cystinuria, favors kidney stone recurrences. Even in these patients, if a core component different from cystine is detected, the patients can benefit from preventive measures targeted on that particular core component as a measure of trying to increase the stone-free period between stone episodes and spare the patients from numerous procedures.

3.2 Clinical approach in future studies

The examination of intact urinary calculi by CSCT analysis reveals the presence of minerals and their spatial arrangement in composition image maps. These composition maps and supplementary knowledge of the interrelationships between various structures in a stone may have a great impact on clinical decision making regarding recurrence prevention plans [22].

Two stones from our clinical study reported by IRS as 100% cystine were imaged by CSCT to also contain a UA core surrounded by a layer of cystine. The proportions of UA were reported by CSCT at 12% and 14% respectively of the entire stone composition. This aspect shows how selected patients suffering of cystinuria, known as having frequent kidney stones recurrences and not many preventive options, may benefit from a recurrence prevention plan targeting UA presence and crystallization in urine. By

interfering with the nucleation process, the periods between recurrent stones episodes may be prolonged in these patients, with clear social and economic positive impact [23].

Social and economic aspects are not the only aspects of clinical management of recurrent urolithiasis. Clinical decisions are usually made based on patient and physician preferences, and efficacy or drawbacks of known therapeutic options. Although most patients are interested in preventing future episodes [18] it is their compliance we know little of. Ultimately, it is the patient desire, lifestyle and history of stone episodes that will indicate if a prophylaxis plan will be followed.

Mixed kidney stones, especially the non-calcareous ones and knowledge of their structural arrangements have been shown to have strong interrelationships with determining the array of metabolic disturbances encountered in those patients [28]. In many cases the existent metabolic disorders help predict the composition of kidney stones in certain patients and vice versa. In this context CSCT composition-imaging analysis may prove of great help in the analysis of mixed stones, thus facilitating the diagnosis of particular metabolic diseases.

A blinded, extended, future clinical trial, with a dual design, CSCT and IRS for composition analysis and in which patients will benefit of recurrence prevention strategies based on either analysis technique is now shown to be possible. Since CSCT and IRS analyses reveal equivalent results on major stone components with CSCT offering in addition detailed structural and compositional analysis, including the core, a future clinical study may demonstrate unequivocally clinical benefits of employing

image-based CSCT in the composition analysis of intact urinary calculi for recurrent stone formers.

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Appendices

Appendix A.Comparison data on 85 patients between CSCT results measured and CSCT results corrected for measurement response matrix (grams).

		CSCT measured (grams)								CSCT corrected for measurement response matrix (grams)						
	Patient #	COD	COM	CP	CPD	UA	MAP	CYS		COD	COM	CP	CPD	UA	MAP	CYS
1	**4**	0.19	0.07	0.50	0.17	0.24	1.83	1.09		0.19	0.05	0.50	0.00	0.13	1.82	0.92
2	**15**	0.15	0.14	0.13	0.17	58.27	8.41	1.19		0.15	0.12	0.13	0.00	57.93	8.40	0.00
3	**17**	1.22	2.08	4.85	0.59	7.77	3.92	36.70		1.22	1.92	4.85	0.17	6.19	3.86	35.77
4	**21**	5.21	34.31	1.25	0.62	0.72	1.52	0.50		5.21	33.63	1.25	0.48	0.65	1.26	0.35
5	**23**	7.35	47.67	4.60	1.44	1.51	1.35	0.74		7.35	46.71	4.60	1.33	1.45	0.98	0.54
6	**24**	0.33	1.10	0.05	0.07	43.08	3.41	6.29		0.33	1.00	0.05	0.00	42.84	3.40	2.57
7	**25**	1.21	1.27	53.11	0.65	5.28	1.68	1.22		1.21	1.11	53.11	0.48	5.19	1.62	0.67
8	**26**	19.50	41.78	12.82	4.65	1.25	0.68	0.84		19.50	39.24	12.82	4.65	1.22	0.00	0.74
9	**27**	21.90	31.24	3.40	1.57	2.04	2.58	1.20		21.90	28.39	3.40	1.41	1.94	1.49	0.92
10	**28**	0.75	1.05	25.19	1.07	4.00	1.01	1.13		0.75	0.95	25.19	0.97	3.93	0.97	0.73
11	**29**	1.00	1.59	24.58	77.84	4.87	1.58	4.69		1.00	1.46	24.58	77.67	4.64	1.53	4.18
12	**32**	0.00	16.47	0.05	0.05	148.21	9.50	20.35		0.00	16.47	0.05	0.00	147.52	9.50	7.73
13	**33**	3.17	61.21	3.87	1.18	2.17	2.50	0.90		3.17	60.79	3.87	0.93	2.05	2.34	0.54
14	**34**	46.80	51.36	72.55	8.44	5.26	14.24	3.23		46.80	45.28	72.55	7.13	4.71	11.90	1.86
15	**35**	37.69	30.84	20.62	4.30	1.65	10.52	1.91		37.69	25.94	20.62	3.35	1.26	8.64	1.08
16	**36**	1.57	2.85	9.28	1.51	15.49	5.79	135.18		1.57	2.65	9.28	0.88	9.93	5.71	133.48
17	**37**	22.05	99.68	12.79	5.43	1.58	7.69	3.53		22.05	96.82	12.79	4.71	1.20	6.58	2.88
18	**38**	0.90	2.18	3.59	0.83	3.43	3.33	34.13		0.90	2.06	3.59	0.47	1.95	3.29	33.59
19	**39**	2.14	34.75	4.06	5.21	3.99	4.67	3.60		2.14	34.48	4.06	4.71	3.69	4.56	2.92
20	**41**	21.76	7.31	10.98	17.75	0.15	4.42	9.51		21.76	4.48	10.98	17.38	0.00	3.33	9.24
21	**42**	26.48	10.05	1.01	13.21	32.70	1.86	20.49		26.48	6.61	1.01	13.15	31.96	0.54	17.83
22	**43**	26.77	16.45	4.44	12.93	0.07	0.06	2.21		26.77	12.97	4.44	12.93	0.00	0.00	2.20
23	**45**	14.43	8.13	0.77	9.86	13.56	0.35	11.15		14.43	6.26	0.77	9.86	13.16	0.00	10.07
24	**46**	0.19	0.04	0.03	0.07	0.01	0.07	0.03		0.19	0.01	0.03	0.06	0.01	0.06	0.02
25	**47**	15.52	13.88	13.73	7.98	4.82	3.34	2.69		15.52	11.86	13.73	7.70	4.63	2.56	2.10
26	**48**	0.91	0.27	0.23	1.20	1.06	0.99	7.20		0.91	0.15	0.23	1.09	0.74	0.94	7.04
27	**49**	10.71	22.59	0.68	1.68	2.11	2.29	0.82		10.71	21.20	0.68	1.48	2.02	1.75	0.51
28	**50**	7.92	3.96	3.23	1.75	0.84	0.39	0.36		7.92	2.93	3.23	1.75	0.82	0.00	0.30
29	**51**	0.36	0.37	1.36	0.47	5.73	1.14	30.31		0.36	0.33	1.36	0.35	4.50	1.12	29.76
30	**52**	1.27	0.23	0.89	23.54	0.43	1.50	0.72		1.27	0.07	0.89	23.38	0.35	1.43	0.57
31	**53**	0.35	0.32	0.71	0.51	2.88	4.68	55.36		0.35	0.27	0.71	0.00	0.51	4.67	54.76
32	**54**	4.50	20.05	0.20	1.39	1.42	1.27	0.77		4.50	19.46	0.20	1.27	1.36	1.05	0.57
33	**55**	0.63	0.63	6.73	84.87	0.29	1.79	5.48		0.63	0.55	6.73	84.68	0.01	1.75	5.32
34	**57**	1.14	10.00	5.87	1.61	5.04	1.32	1.56		1.14	9.85	5.87	1.47	4.95	1.26	1.05
35	**58**	0.09	1.20	0.09	0.10	1.52	1.61	23.57		0.09	0.18	0.09	0.00	0.52	1.69	23.31
36	**60**	15.25	73.40	0.68	5.73	4.59	6.89	3.50		15.25	71.41	0.68	5.05	4.24	6.13	2.64
37	**61**	9.82	5.03	2.05	1.39	0.84	1.97	1.27		9.82	3.76	2.05	1.22	0.73	1.48	1.08
38	**62**	20.90	9.93	3.28	2.51	1.97	1.79	1.08		20.90	7.21	3.28	2.43	1.90	0.74	0.86
39	**63**	21.20	29.53	0.23	2.18	37.68	6.90	1.24		21.20	26.77	0.23	1.54	37.45	5.84	0.00

40	**64**	3.27	20.58	3.50	1.11	2.40	1.38	0.53		3.27	20.15	3.50	0.98	2.34	1.21	0.24
41	**65**	1.58	22.47	0.09	0.57	17.33	6.21	1.30		1.58	22.26	0.09	0.00	17.09	6.13	0.00
42	**66**	4.49	22.19	0.37	0.72	0.82	0.91	0.54		4.49	21.61	0.37	0.65	0.78	0.68	0.42
43	**67**	2.56	1.41	9.44	1.57	4.59	2.65	1.17		2.56	1.07	9.44	1.30	4.47	2.52	0.06
44	**68**	6.50	25.72	0.34	0.79	1.27	1.77	0.79		6.50	24.87	0.34	0.63	1.19	1.45	0.57
45	**69**	0.20	0.34	0.05	0.10	29.67	10.09	1.81		0.20	0.31	0.05	0.00	29.27	10.08	0.00
46	**70**	2.46	5.24	0.28	0.53	0.94	0.85	0.48		2.46	4.92	0.28	0.45	0.90	0.73	0.34
47	**71**	1.00	7.49	0.16	0.39	110.47	41.18	6.26		1.00	7.36	0.16	0.00	108.82	41.13	0.00
48	**72**	0.22	0.06	0.02	0.09	7.21	3.96	1.01		0.22	0.03	0.02	0.00	7.05	3.94	0.12
49	**73**	0.94	0.32	2.56	0.55	1.64	1.05	0.36		0.94	0.19	2.56	0.44	1.51	1.00	0.15
50	**74**	0.01	0.01	0.00	0.00	0.74	0.32	0.04		0.01	0.00	0.00	0.00	0.72	0.32	0.00
51	**75**	0.39	0.27	0.53	0.20	0.44	0.90	0.64		0.39	0.22	0.53	0.11	0.38	0.88	0.54
52	**76**	0.20	0.46	0.51	0.31	7.38	2.13	33.76		0.20	0.43	0.51	0.08	5.98	2.12	33.00
53	**77**	17.82	49.21	32.79	5.63	9.56	4.40	3.16		17.82	46.89	32.79	5.25	9.34	3.51	2.12
54	**78**	19.77	23.20	66.63	3.60	23.11	8.83	8.01		19.77	20.64	66.63	2.73	22.58	7.84	5.54
55	**79**	0.01	0.05	0.00	0.01	11.32	2.68	1.24		0.01	0.04	0.00	0.00	11.21	2.68	0.12
56	**80**	23.24	16.58	1.58	1.62	1.23	2.95	1.35		23.24	13.56	1.58	1.42	1.11	1.78	1.11
57	**82**	2.72	1.25	2.75	1.57	23.60	8.04	448.04		2.72	0.90	2.75	0.70	5.47	7.90	445.52
58	**83**	2.99	6.19	1.03	0.55	475.86	74.50	2.99		2.99	5.80	1.03	0.00	472.89	74.35	0.00
59	**84**	12.34	10.75	1.42	0.49	0.34	1.44	0.20		12.34	9.15	1.42	0.40	0.31	0.83	0.12
60	**85**	1.93	25.53	0.63	0.76	1.53	3.16	0.21		1.93	25.28	0.63	0.43	1.41	3.07	0.00
61	**86**	0.04	0.05	0.00	0.00	0.00	0.00	0.00		0.04	0.04	0.00	0.00	0.00	0.00	0.00
62	**87**	0.10	0.51	0.03	0.04	37.07	12.55	1.39		0.10	0.50	0.03	0.00	36.57	12.54	0.00
63	**90**	2.44	0.32	13.47	0.15	2.77	11.88	0.42		2.44	0.00	13.47	0.00	2.30	11.76	0.00
64	**91**	13.18	25.64	0.24	0.27	0.22	2.49	0.19		13.18	23.93	0.24	0.07	0.14	1.83	0.03
65	**94**	0.01	0.07	0.02	0.01	0.01	0.00	0.00		0.01	0.07	0.02	0.01	0.00	0.00	0.00
66	**95**	0.10	0.13	0.01	0.00	0.00	0.00	0.00		0.10	0.12	0.01	0.00	0.00	0.00	0.00
67	**96**	0.03	0.02	0.02	0.00	0.00	0.00	0.00		0.03	0.01	0.02	0.00	0.00	0.00	0.00
68	**97**	0.01	0.01	0.00	0.00	0.00	0.00	0.00		0.01	0.01	0.00	0.00	0.00	0.00	0.00
69	**99**	0.02	0.16	0.08	0.00	0.01	0.00	0.00		0.02	0.15	0.08	0.00	0.01	0.00	0.00
70	**100**	0.06	0.35	0.02	0.00	0.07	0.02	0.02		0.06	0.34	0.02	0.00	0.07	0.02	0.01
71	**101**	0.00	0.00	0.00	0.00	0.03	0.01	0.44		0.00	0.00	0.01	0.00	0.01	0.00	0.43
72	**102**	0.02	0.22	0.01	0.00	0.00	0.01	0.00		0.02	0.22	0.01	0.00	0.00	0.01	0.00
73	**103**	0.01	0.02	0.01	0.00	0.00	0.00	0.00		0.01	0.02	0.01	0.00	0.00	0.00	0.00
74	**104**	0.00	0.00	0.01	0.04	0.00	0.00	0.01		0.00	0.00	0.01	0.04	0.00	0.00	0.01
75	**106**	0.09	0.02	0.00	0.00	0.00	0.00	0.00		0.09	0.01	0.00	0.00	0.00	0.00	0.00
76	**108**	0.02	0.10	0.01	0.00	0.00	0.01	0.01		0.02	0.10	0.01	0.00	0.00	0.01	0.00
77	**109**	0.08	0.13	0.01	0.00	0.00	0.01	0.00		0.08	0.12	0.01	0.00	0.00	0.00	0.00
78	**110**	0.10	0.14	0.07	0.01	0.02	0.01	0.00		0.10	0.13	0.07	0.01	0.02	0.00	0.00
79	**111**	0.00	0.00	0.00	0.00	0.13	0.05	0.01		0.00	0.00	0.00	0.00	0.13	0.05	0.00
80	**112**	0.11	0.02	0.00	0.00	0.00	0.00	0.00		0.11	0.00	0.00	0.00	0.00	0.00	0.00
81	**113**	0.00	0.00	0.03	0.00	0.00	0.01	0.00		0.00	0.00	0.00	0.03	0.00	0.00	0.01
82	**115**	0.00	0.01	0.02	0.67	0.04	0.05	0.11		0.00	0.00	0.02	0.66	0.03	0.05	0.10
83	**117**	0.00	0.00	0.01	0.00	0.00	0.00	0.00		0.00	0.00	0.01	0.00	0.00	0.00	0.00
84	**118**	0.02	0.01	0.00	0.00	0.00	0.00	0.00		0.02	0.00	0.00	0.00	0.00	0.00	0.00
85	**119**	0.00	0.01	0.43	0.01	0.06	0.02	0.03		0.00	0.01	0.43	0.00	0.05	0.01	0.03

Appendix B.Comparison data on 85 patients between CSCT results and IRS results, both expressed in percentages.

		CSCT (corrected)								IRS						
		COD	COM	CP	CPD	UA	MAP	CYS		COD	COM	CP	CPD	UA	MAP	CYS
1	**4**	5	1	14	0	4	50	26		40	60	0	0	0	0	0
2	**15**	0	0	0	0	87	13	0		0	20	0	0	80	0	0
3	**17**	2	3	9	0	12	7	67		0	0	0	0	0	20	80
4	**21**	12	78	3	1	2	3	1		10	90	0	0	0	0	0
5	**23**	12	74	7	2	2	2	1		10	90	0	0	0	0	0
6	**24**	1	2	0	0	85	7	5		0	0	0	0	80	20	0
7	**25**	2	2	84	1	8	2	1		0	0	100	0	0	0	0
8	**26**	25	50	16	6	2	0	1		30	70	0	0	0	0	0
9	**27**	37	48	6	2	3	3	1		20	80	0	0	0	0	0
10	**28**	2	3	75	3	12	3	2		0	0	100	0	0	0	0
11	**29**	1	1	21	68	4	1	4		0	0	0	100	0	0	0
12	**32**	0	9	0	0	81	5	5		0	0	0	0	80	20	0
13	**33**	4	83	5	1	3	3	1		10	90	0	0	0	0	0
14	**34**	25	24	38	4	2	6	1		65	0	35	0	0	0	0
15	**35**	38	27	21	3	1	9	1		0	95	5	0	0	0	0
16	**36**	1	2	6	0	6	3	82		0	0	0	0	0	0	100
17	**37**	15	66	9	3	1	4	2		20	80	0	0	0	0	0
18	**38**	2	5	8	1	4	7	73		0	0	0	0	0	0	100
19	**39**	4	61	7	8	7	8	5		40	60	0	0	0	0	0
20	**41**	32	7	16	26	0	5	14		0	0	10	0	0	90	0
21	**42**	27	7	1	14	32	1	18		0	0	0	0	100	0	0
22	**43**	45	22	7	22	0	0	4		20	80	0	0	0	0	0
23	**45**	27	11	1	18	24	0	19		10	90	0	0	0	0	0
24	**46**	48	3	6	17	3	16	7		65	0	35	0	0	0	0
25	**47**	27	20	24	13	8	4	4		65	0	35	0	0	0	0
26	**48**	8	1	2	10	7	8	64		0	0	0	0	0	0	100
27	**49**	28	55	2	4	5	5	1		10	80	0	0	0	10	0
28	**50**	47	17	19	10	5	0	2		95	5	0	0	0	0	0
29	**51**	1	1	4	0	12	3	79		0	0	0	0	0	0	100
30	**52**	5	0	3	84	1	5	2		0	0	0	100	0	0	0
31	**53**	0	0	1	0	1	8	90		0	0	0	20	0	0	80
32	**54**	16	69	0	4	5	4	2		10	90	0	0	0	0	0
33	**55**	1	1	7	85	0	1	5		0	0	0	100	0	0	0
34	**57**	4	39	23	6	19	5	4		10	80	10	0	0	0	0
35	**58**	0	1	0	0	2	7	90		0	0	0	0	0	0	100
36	**60**	14	68	1	5	4	6	2		10	90	0	0	0	0	0
37	**61**	49	19	10	6	4	7	5		65	0	35	0	0	0	0
38	**62**	56	19	9	7	5	2	2		95	5	0	0	0	0	0
39	**63**	23	29	0	2	40	6	0		0	50	0	0	50	0	0
40	**64**	10	64	11	3	7	4	1		0	95	5	0	0	0	0
41	**65**	3	47	0	0	37	13	0		0	60	0	0	40	0	0

42	**66**	16	75	1	2	3	2	1		10	90	0	0	0	0	0
43	**67**	12	5	43	6	20	11	3		0	0	100	0	0	0	0
44	**68**	18	70	1	2	3	4	2		10	90	0	0	0	0	0
45	**69**	0	1	0	0	74	25	0		0	0	0	0	100	0	0
46	**70**	25	49	3	4	9	7	3		95	5	0	0	0	0	0
47	**71**	1	4	0	0	69	26	0		0	0	0	0	100	0	0
48	**72**	2	0	0	0	62	35	1		0	0	0	0	100	0	0
49	**73**	14	3	37	6	23	15	2		0	0	100	0	0	0	0
50	**74**	1	0	0	0	68	31	0		0	0	0	0	100	0	0
51	**75**	13	7	17	3	13	29	18		0	0	10	0	0	90	0
52	**76**	1	1	1	0	14	5	78		0	0	0	0	0	0	100
53	**77**	15	40	28	4	8	3	2		10	90	0	0	0	0	0
54	**78**	14	14	46	2	15	5	4		0	0	100	0	0	0	0
55	**79**	0	0	0	0	80	19	1		0	0	0	0	100	0	0
56	**80**	53	31	3	3	3	4	3		10	90	0	0	0	0	0
57	**82**	1	0	1	0	1	1	96		0	0	0	0	0	0	100
58	**83**	0	1	0	0	85	14	0		0	0	0	0	80	20	0
59	**84**	50	38	6	2	1	3	0		20	80	0	0	0	0	0
60	**85**	6	78	2	1	4	9	0		0	95	5	0	0	0	0
61	**86**	40	50	3	5	1	0	1		40	60	0	0	0	0	0
62	**87**	0	1	0	0	74	25	0		0	0	0	0	100	0	0
63	**90**	8	0	45	0	8	39	0		0	0	20	0	0	80	0
64	**91**	33	61	1	0	0	5	0		10	90	0	0	0	0	0
65	**94**	12	58	20	5	4	1	0		10	90	0	0	0	0	0
66	**95**	41	50	6	1	1	0	1		20	80	0	0	0	0	0
67	**96**	45	16	31	3	1	1	3		30	60	10	0	0	0	0
68	**97**	40	31	10	10	6	0	3		65	0	35	0	0	0	0
69	**99**	9	58	30	0	2	1	0		15	70	15	0	0	0	0
70	**100**	12	66	3	0	14	3	2		0	80	0	0	20	0	0
71	**101**	0	0	0	0	2	0	98		0	0	0	0	0	0	100
72	**102**	7	81	5	1	1	5	0		0	100	0	0	0	0	0
73	**103**	15	45	30	3	3	2	2		0	80	10	0	0	10	0
74	**104**	3	1	20	57	5	6	8		0	0	0	80	0	20	0
75	**106**	87	8	2	1	1	0	0		30	60	10	0	0	0	0
76	**108**	17	68	7	0	1	4	3		10	90	0	0	0	0	0
77	**109**	38	56	3	1	1	0	1		20	80	0	0	0	0	0
78	**110**	31	41	21	2	5	0	0		40	60	0	0	0	0	0
79	**111**	0	2	0	0	70	28	0		0	0	0	0	100	0	0
80	**112**	93	4	0	2	1	0	0		80	20	0	0	0	0	0
81	**113**	0	0	72	0	0	22	6		0	0	30	0	0	70	0
82	**115**	0	1	2	76	3	6	12		0	0	0	100	0	0	0
83	**117**	16	22	55	0	0	7	0		0	80	20	0	0	0	0
84	**118**	70	14	3	3	0	7	3		40	60	0	0	0	0	0
85	**119**	0	2	79	1	10	3	5		0	0	100	0	0	0	0

Curriculum Vitae

Name: Cristian Dihel

Post-secondary Education and Degrees:
The University of Medicine and Pharmacy
Timisoara, Timis, Romania
1993-1999 Bachelor of Medicine

The University of Western Ontario
London, Ontario, Canada
2009-2012 M.Sc.

Honours and Awards:
The University of Medicine and Pharmacy Timisoara
Scholarship for academic excellence 1994-1999

Practice Licence in Medicine
College of Physicians of Romania
2000

Related Work Experience
Intern Physician/General Practitioner
The University Hospital, Arad, Romania
2000-2002

Clinical Advisor in Metabolic Disorders
Sandoz/Novartis Group, Bucharest, Romania
2002-2004

Chart reviewer in clinical trials
The University of Western Ontario, London, Ontario
Centre for Studies in Family Medicine
2011-2012

Publications:

C. Dihel, I.A. Cunningham
CSCT for core composition analysis of urinary calculi-
Prospective clinical benefits – Poster Presentation
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