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Prediction of the Chemical Composition of Urinary Calculi Using CT

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List of abbreviations

COM	Calcium oxalate monohydrate stone
CT	Computed tomography
HU	Hounsfield unit
HA	Hydroxyapatite stone
IN	Infrared spectroscopy
IVU	Intravenous urography
KUB	Kidney , Ureter , Bladder plain film
KV	Kilo-volt
MA	Milliamper
NCHCT	Noncontrast helical CT
ROI	Region of interest
UA	Uric acid stone
US	Ultrasound scan

Abstract:
Purpose: Our objective for this study was to determine the precision of spiral CT in identifying the chemical composition of different types of urinary calculi with measurement of absolute HU values of region of interest (ROI)using unenhanced spiral CT.

Materials and methods :A total of (50) urinary stones, obtained from patients who underwent open surgery ,were scanned with a multidetector row scanner using (2) mm collimation at energy level of (120) kV at (200) mA .Two post-scanning protocols were used for the HU value assignment ,tissue and bone windows. In both protocols ,three transverse planes were defined in each stone , one near the top, one in the middle ,and one near the bottom. Three regions of interest (ROI) were obtained in each plane .The absolute HU value was determined by three methods :the mean of nine ROI ,the mean of the central three ROI ,and the central ROI in the middle plane .Determination of the stones composition was performed using the absolute HU value measured at (120) kV .All stones were analyzed by infrared spectroscopy to determine their chemical composition.

Results : the calculi classified into groups according to their chemical composition .A total of 50 calculi ,include (34) pure stones[(14)uric acid (UA), (15) calcium oxalate monohydrate (COM), (5) Struvite] ,and (16) mixed stones [(7) COM +hydroxyl apatite (HA), (4) COM +uric acid, (5) mixed Struvite + COM + hydroxyapatite] were included in the statistical analysis. Using the absolute HU values at (120) k V , we could distinguish ,with statistical significance ,all pure types from each other ,from the least to the most dense , the pure stone types were UA , struvite ,COM . Mixed UA + COM calculi were more dense and significantly different from pure UA but insignificantly different from Struvite , Struvite and COM can differentiated from each other but there were insignificant differences between them and mixed stones (COM+UA and struvite+COM+HA) . Mixed COM + HA stones were the most dense stones and can differentiated from other types.

Conclusion :This study suggest that the measurement of absolute HU values at a single energy level utilizing CT scanning with small collimation size can uncover significant differences among all pure stones and insignificant for mixed stones.

CHAPTER ONE

Introduction:

Epidemiology of stone disease:

Stone disease accounts for more than 400,000 hospitalization annually. The peak incidence is in the third to fifth decades. Males are affected 3 times as commonly as females and whites 4 to 5 times as commonly as blacks. In a patient who has passed one stone ,the like hood of passing another stone is about 15% by 3 years and 30 -50% by 15 years. Urolithiasis is a lifelong disease with an average of 9 years intervening between episodes [1,2].

Etiology and pathogenesis

Development of stones in the urinary tract is a complex , poorly under- stood, multifactorial process .
-Genetic/heredity ; the urinary stones is associated with a polygenic defect and partial penetrance . Conditions of

increased incidence: Cystinuria –autosomal recessive, Renal tubular acidosis-type 1, Medullary sponge kidney .
–Diet; ingestion of excessive amount of purines, oxalate , calcium, phosphate lead to excessive excretion of these components in urine.
–Geography; increased incidence in areas of high temperature / humidity , so stone is higher in those who live on mountains, deserts and tropical areas.
–Occupation; increased incidence in administrative and sedentary personal than in manual workers.
–Climatic and seasonal factors ; higher incidence of stones in the summer months . Increase perspiration lead to concentrated urine and increase in urinary crystallization [3].
-Water intake ; increased water intake and increased urinary output decrease the incidence of urinary calculi in those patients who are predisposed to the disease . Two factors involved the relationship between water intake and urolithiasis are (1) the volume of water ingested as opposed to that lost by perspiration and respiration and (2) the mineral content of the water supply of the region [some state that excessive water hardness (e.g. by sodium carbonate) causes a greater incidence of stone disease] [1].
-Renal infection; the predominant bacteria found in the nuclei of urinary stones are staphylococci and E. coli . Stone formation are common when urine infected with urea splitting streptococci ,staphylococci and particularly Proteus sp. .
-Urinary stasis ; like PUJ stenosis and medullary sponge kidney.
–Prolong immobilization ; e.g. paraplegia , is liable to result in skeletal decalcification with increase in urinary calcium .
–Hyperparathyroidism ; leading to hypercalcaemia and hypercalciuria is found in 5% or less of those who present with radio- opaque calculi. In case of recurrent or multiple stones , this cause should be eliminated by appropriate investigations.
-Randall"s plaque ; Randall suggested that the initial lesion in some cases of kidney stone was an erosion at the tip of a renal papilla . Deposition of calcium on this erosion produced which has been called Randall's plaque . It has further been shown that minute concretions (microliths) regularly occur in the renal parenchyma and Carr postulated that these particles are carried by the lymphatics to the sub endothelial region where they may accumulate . Ulceration of the epithelium exposes the potential calculus to the urine with the result that a stone forms[3].

Stone Types

1. Calcium oxalate stones : about 70% of all stone types especially in Middle East . It occurs in three crystalline forms : Calcium oxalate monohydrate (COM) , dehydrate (COD) and trihydrate (COT). Most calcium oxalate stones are composed of pure type (33% of stone) or combination calcium oxalate and calcium phosphate (34%). Calcium stones may develop as a result of excessive excretion of calcium (hypercalciuria), decrease urinary volume , hyperparathyroidism , uinary PH<6 , congenital abnormalities , dietary habits, hot climate and presence or absence of inhibitors[4].
2. Uric acid stones: about 10 - 20% of urinary stones , it crystallizes in monoclinic system. It affects middle age men more than young adults. Persistent urinary acidity , decrease urinary volume , hyperuricosuria , and increase protein level in the diet may be the main causes of uric acid stones. Inborn errors of metabolism can cause uric acid stones in children. Uric acid poorly soluble at PH <5.5[4].
3. Phosphate stones : 10-15% of urinary stones. Five types ; hydroxy- apatite , Struvite , brushite , whitlokite and newbeyrite. The main bulk are Apatite and Struvite [magnesium ammonium phosphate and carbonate apatite-triple phosphate = 15% of urinary stones]. Brushite occurs in1-2% of stones. The other two occur rarely . Phosphate stones are more common in females , it is thought to be caused by infection . In children, it may occur because of anatomical defect . The stone grow rapidly to a large size in presence of an alkaline urine (PH>7) and urease producing bacteria in the urine [4].
4.Cystine stones : are uncommon (1-3% of stones). It crystallized in hexagonal system and occurs as a result of Cystinuria caused by inborn error of metabolism , so it occurs in early age in equal ratio and it may occur in the age of 20-30 years. Increasing PH>7.5 will increase cystine secretion[4].
5.Other types;1 % incidence ; Xanthin stones : may be found in children and adult of different ages , Silicate stones : rare in human kind, Triamterene stones , Indinavir stones : in patient with HIV infection treated by indinavir drug [1] .
6.Mixed stones ; are those types of stones consisting of two or more of the above-mentioned types[1].

Stone fragility

The concept of stone fragility was first introduced by Dretler (1988) [5] . The ease with which a stone is fragmented by ESWL varies among stones of different compositions . Furthermore , stones of same composition may fragment differently .The holmium laser in vitro was most effective in treating struvite stones and least effective in the treatment of calcium oxalate monohydrate stones. These results appear to correlate the thermal threshold for each stone composition . Cystine and brushite stones are the most resistant to ESWL ,followed by calcium oxalate monohydrate stones . Next , in descending order , are hydroxyapatite , struvite ,calcium oxalate

dihydrate ,and uric acid stones . Stone composition can also affect the type of fragments produced[1].

Generally ,stones that fragment with difficulty (i.e., brushite , cystine , calcium oxalate monohydrate) should be treated with ESWL only when they are small (i.e., less than 1.5 cm) .Larger stones are preferentially with PNL or RIRS (retrograde ureteroscopic intrarenal surgery) . The ability to predict stone composition and, cosequently , the number of shock waves required for complete stone fragmentation would be of benefit in selecting appropriate treatment for stone patients .However , except for cystinuric patients and patients who have had previous stone analysis, accurate prediction of stone composition based on imaging and patient history is difficult[1] .

Using x-ray patterns to stone fragility , smooth edged stones a homogenous structure needed significantly more shock waves to be completely fragmented compared with round , radially reticulated stones with speculated edges and stones with an irregular margin and structure .

However , in prospective study , the overall accuracy of predicting stone composition from plain radiographs was reported to be only 39% and , thus , insufficient for clinical use [1].

The emergence of noncontrast CT (NCCT) in the assessment of renal colic has led to a growing interest in comparing NCCT attenuation coefficient measurements with stone composition .

Mostafavi and associates (1998 b) , in an in vitro study using spiral CT absolute attenuation values at two energy levels , were able to predict accurately the chemical composition of pure urinary calculi[6] .

Likewise , Saw and associates (2000 b)found that CT at 1 mm collimation (120 kV)was able to differentiate in vitro between stone groups (each containing at least 60% of one stone constituent) based on absolute attenuation values [7] .A definite effect of stone size on attenuation measurements and a dramatic effect of beam collimation width on measured attenuation were noted .

Furthermore , CT attenuation values in vitro may predict fragility of calcium stones . Although composition of cystin , uric acid and struvite stones can usually be predicted based on the patient's clinical presentation , the ability to differentiate preoperatively between subgroups of calcium oxalate stones and to predict stone fragility would be a major advance in selecting patients for ESWL or alternative treatment modalities . Unfortunately , most stones are not pure in composition . Because the density and shape of a stone can be altered by the amount of each crystalline component , data are insufficient to assess the usefulness of CT in predicting stone composition in the clinical setting ,particularly for calcium oxalate stones[1].

Early Generation CT Scanner

The application of helical CT technology for the diagnosis and management of urinary calculus disease is altering dramatically the practice of urology and diagnostic uroradiology , which had traditionally relied upon plain radiography of the kidney ,Ureter , and bladder(KUB) , intravenous urography (IVU) , or ultrasound (US) to evaluate calculus disease[8]. The first CT scanner , the EMI Mark I (London, England) ,was used in 1972 . Unlike plain- film tomography , in which a image is created of a thin focused section by blurring out the image of other areas , a CT image is reconstructed only from data of the region of interest .

The cross- section created is usually transverse (axial) , although newer scanners have capability of choosing any plane . The image is a reconstructed two- dimensional array of quantized gray-scale values or pixel . Each pixel is a two –dimensional weighted average of the sum of the gray scale values in the three-dimensional voxel . The pixel values are related directly to the linear-attenuation coefficients , μ , which in turn is related directly to the effective energy of the photon beam passing through and not absorbed by the patient. A pixel value , also known as a CT number or Hounsfield unit (HU) , is converted to a gray –scale value and then displayed[9] .

There are 2^{12} or 4096 different gray –scale values , which range from -1000 to 3096 HU . Because different tissues , fluids , and objects consist of different elemental compositions , they produce different x-ray attenuations .

By convention, standard pixel values exist for certain tissue densities: water = 0, air = -1000 , fat = -80 to -100 , soft tissue = 10 to 80 ,and bone = 400 to 3000 .Only 256 gray scale values, however, can be displayed.

A window of gray scale values must be chosen to highlight a range of tissue densities , for instance a soft – tissue window or a bone window . Tissues with a CT number less than the lower limit of the window all appear radiolucent (black) , and those with a CT number greater than the upper limit appear radio opaque (white) . This explains why all calculi appear equally dense on CT , because even the least dense , non calcified uric- acid calculus typically has a CT number between 400 and 600 , well above the densest gray –scale value on the standard display window[10].

Helical CT *:*

Helical CT , first used clinically in 1989 , has expanded the practical application of CT by overcoming fundamental technical constraints of standard CT . Helical or spiral CT refers to the shape of the path that the x-ray focus follows around the patient [11]. The basic advantages of NCHCT scanning over other imaging methods include

(a) high sensitivity and specificity in the detection of ureteral and renal stones For renal stone sensitivity 96% , and specifity 99% . For ureteric stone sensitivity 94%,and specifity 97% (compared to US : sensitivity

19% ,and specifity 97% while IVU : sensitivity 52% ,and specifity 94% [12].

(b) speed, because the entire examination can be performed within only a few minutes and eliminates potential delays encountered with excretory urography if ureteral obstruction is present and contrast is delayed in its entrance into the collecting system;

(c) safety, because the examination is performed without the use of iodinated contrast material and eliminates the risks of contrast , which include allergic reactions and toxicity ;

(d) detection of non urological pathology , because many patients presenting with suspected ureteral colic have other disease process, such as appendicitis or ovarian cysts , and NCHCT is the only imaging technique used for suspected colic that detects these other pathologic conditions;

(e) cost, because NCHCT can be priced at a level competitive with excretory urography and ultrasound because of the short table tie needed and the lack of contrast ;

(f) and ability to detect all stones regardless of composition. Stones, such as cystine and uric stones , that are barely visible or invisible on routine radiographs have sufficient density to be demonstrated clearly with CT scanning . The only stones not detected are those associated with indinavir therapy for HIV infections[13].

With experience , spiral CT outperforms all other available studies in the evaluation of urinary-tract stones . The technique has been made possible by the development of the spiral or helical CT scan , which scans the entire abdomen and pelvis in one or two held breaths and virtually eliminates the problem of respiratory motion. The patient is in continuous motion through the scanner as the data is acquired , and a column of data is acquired that then can be reconstructed to create axial images[14] . Spiral CT allows three-dimensional reconstruction , which can be used in the evaluation of stone disease .

Hubert et al found this technique helpful in evaluation of staghorn calculi prior to percutaneous nephrostolithotomy (PCNL) , because it showed the precise shape of the stone and its branches , they felt three-dimensional reconstruction allowed for better pretreatment planning . They also used this technique to better define the size and shape of uric acid stones , so that changes with medical therapy could be followed[15].

Stone Density

Recently , the use of non contrast spiral CT (NCCT) has gained widespread acceptance in the evaluation of urinary stone patients . It has long been used clinically to evaluate the causes of radiolucent filling defects using Hounsfield units (HU) to distinguish calculi from tumors or blood clots , and to identify non urological causes of flank pain [16,17,18]. Urinary stones have a significantly higher CT attenuation than the surrounding soft tissues and are virtually always visible on NCCT [17,18,19,20].

Accurate determination of stone composition usually requires chemical stone analysis . CT may be able to identify stone composition more accurately based on measurement of stone density.

Investigators have attempted to determine whether CT numbers could determine accurately the chemical composition of calculi . Before the widespread use and availability of extracorporeal shock- wave lithotripsy ,ureteroscopy , and percutaneous nephrolithotomy , calculus composition was a consideration only for determining whether to use chemolysis rather than a surgical approach to selected calculi[21].

With the introduction of these newer modalities , the fragility of a calculus became a clinical consideration . Attempts to diagnose calculus composition by radiographic patterns were inexact [22].

Several in vitro studies have suggested that NCCT can demonstrate & measure differences in radio density among different urinary stones [6,23,24].

-Federle et al showed that CT numbers obtained in vitro were not significantly different from those obtained for the same calculus in vivo[19].

-Newhouse et al scanned 30 chemically pure and 5 mixed – composition calculi in vitro . They found that the relative densities of the calculi were accurate; however, there was significant overlap between types of calculi ,especially mixed calculi .Although in vitro and in vivo CT numbers do not differ significantly , the assignment of a CT number to a calculus has a number of variables that interfere with reproducibility and standardization [25].

-Hillman et al showed that mean pixel values and their standard deviations could differentiate the three most commonly encountered calculus compositions-uric acid , calcium oxalate, and struvite with 89% overall accuracy[23].

-Mitcheson et al used three density parameters in an effort to determine composition . They scanned the calculi in vitro at two different voltages ,recorded the CT numbers , and subtracted the two numbers [23] .

Using mathematic modeling to show that most calculi should be distinguishable (except struvite and cystine) by using histograms (densities of individual pixels are selected by a region-of-interest cursor and displayed either as a grid of CT number or histogram) and these dual –voltage CT values.

By using these new parameters all calculus composition can be differentiated , except for brushite , calcium oxalate , and high calcium content struvite , all of which are in the higher range for CT numbers . Recently , dual-voltage parameters were shown to reliably differentiate all calculus types from each other[17].

There is often significant overlap of CT numbers , however , for cystine, struvite, and low density calcium

oxalate dihydrate and apatite calculi . The majority of calculi are not chemically pure and therefore, are likely to fall within intermediate CT number ranges. Therefore, at this point , the CT number may be thought of as indicating a relative fragility index ,rather than an exact chemical composition[8].

Computed tomographic number may have great utility in planning an intervention , allowing the clinician to be more selective in choice of therapy . As discussed previously , the CT numbers at the high and low ends of the scale permit an approximation of the calculus fragility. The range and distribution of densities also may be of value . A CT number can identify a dissolvable uric acid calculus (400-600 HU) , a very dense calcium-containing calculus (calcium oxalate mono hydrate , brushite) that may not be amenable to shock wave lithotripsy (more than 1200 HU), and a calculus with mixed composition whose therapeutic approach may be in question. For instance , for lower-ureteral calculi , in which shock wave lithotripsy and ureteroscopy are acceptable treatment modalities, low pixel density would incline one toward shock wave lithotripsy , high pixel density toward ureteroscopy[8]

Knowing the composition of a urinary calculus is frequently a key factor in determining its most appropriate management. Should the urine be alkalinized? Will the stone amenable to extra corporeal shock wave lithotripsy (ESWL) , or should ureteroscopy or percutaneous lithotripsy be attempted?

Different techniques have been used to assist in determining the correct chemical composition of calculi .Urine PH, urinary crystals ,prior stone history, the presence of urea splitting organisms , and plain radiography are tools which might be used to infer stone composition [26] .

With these clinical problems in mind, we sought to determine whether the composition of urinary calculi could be predicted by their in vitro CT characteristics in an attempt to find out the best technique for distinguishing the various stones composition , provided that it is clinically practical and would not require repeated imaging of the patients.

Analysis of urinary stones

Most medical therapy for stone disease is now based on analysis of calculi and decisions about proper procedures for treatment require knowledge of stone composition[5]. There are three reasons of carrying out chemical and physical analyses for urolithiasis patients: 1.To diagnose the kind of urolithiatic process. 2.To control therapy . 3.To understand the genesis of urinary calculi[26].

I-Chemical analysis of renal calculi has been all but abandoned . Significant error may occur because qualitative and semi quantitative chemical analysis methods are not accurate[27] .

II-Physical methods have more advantage than the chemical methods in the analyses of the urinary calculi .

These advantages are : 1 . The physical methods require less sample mass (1 mg) than that required by the chemical methods (5 mg) i.e. in the physical methods less size stone can be analyzed .

2 . The physical methods give information about the crystalline phases of the stone , which can't obtained by the chemical methods .

3 . The physical methods can distinguish the different minerals of the stone more accurately than by the chemical methods [34].

The physical methods include :

1.Thermal analysis needs relatively more sample but can give quantitative results.

2.Optical methods give only qualitative results but can analyze small samples .

3.X-ray diffraction technique allows some minor components of mixed urinary calculi to go undetected in as many as 20% to 30% of stones .

4.Spectrometric identification of chemical compound :- (a)Mass , (b)Infrared , (c) Nuclear magnetic resonance , and (d) Ultraviolet spectra . Essentially , the molecule is perturbed by these energy probes and the molecule's responses are recorded as spectra .

Polarizing microscopy ,x-ray diffraction , and infrared spectroscopy are all acceptable techniques for analyzing renal stones.

Stone analysis by infrared spectroscopy

Infrared spectroscopic analysis of urinary calculi can detect crystalline and amorphous minerals[28]. It can perform semi quantitative analysis on a small volume of stones. It can identify "unexpected" stone constituents[29]. The principle of infrared spectroscopy is measurement of the wavelength of electromagnetic energy absorbed by the vibration of atoms in ions or molecules; this procedure is specific for atom groups . Molecular composition and crystal structure influence the absorption and resulting spectra are characteristic of each compound or mixture [30].

The infrared analysis is an easy and rapid procedure ,able to identify all crystalline, amorphous or poorly crystalline components , mineral and organic molecules ,and to distinguish between various crystalline phases of a given substance , moreover it is possible to quantify the relative proportion of the constituents in a mixed stone , the resulting spectra where identified by comparison with published references data and with IR table (atlas)[31]

For determination of identity and purity of chemicals, infrared spectroscopy (IR) has played a special rule in research and technology for more than 25 years . This applies both to qualitative and quantitative analysis of

substances or mixtures and for the structural analysis of chemical compounds .

Depending on the chemical bounding conditions , and also on the particular structure , every chemical molecule has a characteristic absorption spectrum in the infrared region , the "finger print of the molecule [32,33] .

Crystalline components of urinary stones

Component	Formula	Mineralogical name
Calcium oxalate monohydrate	CaC4O4.H2O	Whewellite
Calcium oxalate dihydrate	CaC2O4.2H2O	Weddelite
Magnesium ammonium phosphate hexahydrate	MgNH4PO4.6H2O	Struvite
Magnesium ammonium phosphate monohydrate	MgNH4PO4.H2O	Dittmarite
Calcium hydrogen phosphate dihydrate	CaHPO4.2H2O	Brushite
Carbonate-apatite	Ca10(PO4CO3)6(OH)8	Carbonate-apatite
Hydroxyl-apatite	Ca10(PO4)6(OH)2	Hydroxyl-apatite
Anhydrous tricalcium phosphate	Ca3(PO4)2	Whitlokite
Magnesium dibasic phosphate trihydrate	MgHPO4.3H2O	Newbeyrite
Uric acid	C5H4N4O3	Uric acid
Uric acid dihydrate	C5H4N4O3.2H2O	Uric acid dihydrate
Sodium acid urate	NaC5H3N4O3.H2O	Sodium acid urate
Ammonium acid urate	NH4C5H3N4O3.H2O	Ammonium acid urate
Cystine	C6H12N2O4S2	Cystine
Xanthene	C5H4N4O2	xanthene

Aim of the study

To report an in vitro evaluation of urinary calculi obtained from patients who underwent open surgery ,using infrared spectroscopy for accurate determination of stones chemical composition, and assess the ability of unenhanced helical CT to predict chemical composition of these stones based on measurement of stone attenuation by a CT number or hounsfield unit(HU).

CHAPTER TWO

Material and methods

1.Samples collection and preparation :

During the period from May 2015 to March 2016 , (50) urinary stones obtained from patients who had undergone pyelolithotomy , nephrolithotomy ,or ureterolithotomy at Alhussein teaching hospital in Thi-Qar .

2. Sample preparation for CT scanning:

Each stone sample was washed with distilled water, dried in room temperature.

Each calculus fixed to the CT scanner table free to air with the axial position was adjusted such that a single transverse plane passed through the widest part of the stone.

The calculi were scanned with a multidetector row scanner (Siemens somatom+4) in Alhussein teaching hospital using (2) mm collimation at energy level (120)KV . The mA were kept constant at (200) . Two post-scanning protocols were used for HU value assignment , tissue window (width 350,level 50) and bone window (width 1.200, level 200). Three transverse planes were defined in each stone, near the top , near the bottom , and a plane passed through the widest transverse diameter of the stone. Three regions of interest (ROI) were obtained for each plane (one central and two at the periphery) for tissue and bone window at(120) KV.

The absolute HU values of each stone is presented by three methods ;the mean of the nine ROI ,the mean of the central three ROI ,and central ROI of the plane that pass through the maximum transverse diameter. Distinguishing the chemical composition of the various stones was performed using the absolute HU value measured at (120)KV, in tissue and bone windows separately .

3.Sample preparation for infrared spectroscopy:

All stones were analyzed by the laboratory of sciences college / chemistry department in Al-Nahrein university using Shimadzu FTIR 8000 series . Each stone was ground into fine powder and each sample powder of (1) mg mass was mixed with 100 mg of potassium bromide (KBr) powder in a agate mortar , this mixture was then

pressed with a compression machine to form a transparent pellet (13mm) in diameter . The pellet was mounted in a holder and placed in infrared beam of the spectrometer . The spectral region ranged from 4000-200cm^{-1} in wave number. The absorption spectrum were compared with standard published reference to identify the components of the samples.

Statistical analysis

Independent sample Student's *t*-test was used for comparism of absolute HU values of different types of calculi in both post-scanning protocols.

Pearson correlation was used to determine the correlations between different HU values .Results were considered significant when p <0.05.

CHAPTER THREE

Results

The calculi were classified into groups according to their chemical composition. A total 50 calculi were included in the statistical analysis .

There were 34 pure stones [14 uric acid , 15 calcium oxalate monohydrate, 5 struvite] , 16 mixed stones [4 calcium oxalate monohydrate (COM) + uric acid (UA) ,7 COM +hydroxyapatite (HA) ,5 struvite (St) +COM +HA] .

The absolute HU values derived from ROI (all nine ,central three ,and the ROI of center of the stone) of the two protocols (tissue and bone windows) for all stones of different types are shown in Tables 1- 6 .Table 7 show the mean absolute HU value and standard deviation for each type of stones [also see figures 1= 6]

From the least to the most dense ,the pure stone types were UA (398-421), struvite(642-1029), and COM (1128 -1280).Mixed COM+HA (1456 -1568) had the highest HU values can differentiated from all other stones . Mixed COM +UA had significantly higher HU values than UA , but not significantly different from pure struvite .Mixed struvite+COM+HA , there were no significant difference from either pure COM or struvite .

The highest absolute HU values at 120 k V were those derived from the central three ROI then that derived from the ROI of the stone center .The absolute HU values of the bone window protocol were higher than those of the tissue window protocol .

Tables 8,9,10 represent the p values for the differentiation of stone composition using the absolute HU values at 120 k V in both tissue and bone protocols as following :

1- UA STONE:

A-In tissue window
I-All nine ROI :can differentiated from all types of stones pure and mixed
II-Central 3 ROI :can differentiated from all types of stones except COM+UA(p 0.105)
III-ROI of center :can differentiated from all other types of stones
B-In bone window
I-All nine ROI :cannot differentiated from struvite(P 172)and mixed Struvite +COM +HA(P 0.197)
II-Central 3 ROI :Can differentiated from all except COM+UA (P 0.206)
III-ROI of center :can differentiated from all stones

2- COM STONE :

A-In tissue window
I-All nine ROI :Can not differentiated from struvite(p 0.063) and St+COM+HA
II-Central 3 ROI :Can differentiated from all except from St+COM+HA
III-ROI of center :Can only differentiated from UA(p 0.000) and from COM+UA(p 0.004)
B-In bone window
I-All nine ROI :Can differentiated from all other stones
II-Central 3 ROI :Can differentiated from all other stones
III-ROI of center: Can differentiated from all except COM+HA(p 0.387) and St+COM+HA (p 0.904)

3-STRUVITE STONE :

A-In tissue window
I-All nine ROI :Can differentiated from COM and COM+HA but not from others
II-Central 3 ROI :Can differentiated from all others except COM+UA
III-ROI of center :Can differentiated from all others except COM+UA
B-In bone window
I-All nine ROI :Can differentiated only from COM+HA(p 0.000)
II-Central 3 ROI :Can differentiated from others except from COM+UA (p 0.276) and St+COM+HA(p 0.929)
III-ROI of center :Can differentiated only from UA(p 0.000)and COM+UA (p 0.038)

4-COM+UA

A- In tissue window
I-All nine ROI :Can differentiated from other except St (p 0.554)and St+COM +HA(P 0.480)

II-Central 3 ROI :Can not differentiated from UA (*p* 0.206)and St (*p* 0.276)
III-ROI of center :Can differentiated from all other stones
B-In bone window
I-All nine ROI :Can differentiated from all except St(*p* 0.318) and St+COM+HA(*p* 0.291)
II-Central 3 ROI :Can differentiated only from COM (*p* 0.001) and COM+HA(*p* 0.000)
III-ROI of center :Can differentiated from all except St (*p* 0.248)
5-COM+HA
A-In tissue window
I-All nine ROI :Can differentiated from all other stones
II-Central 3 ROI :Can differentiated from all other stones
III-ROI of center :Can only differentiated from UA (*p* 0.000) and COM +UA(*p* 0.001)
B-In bone window
I-All nine ROI :Can differentiated from all other stones
II-Central 3 ROI :Can differentiated from all other stones
III-ROI of center :Can only differentiated from UA(*p* 0.000) and COM+UA(*p* 0.000)
6-St+COM+HA
A-In tissue window
I-All nine ROI :Can only differentiated from COM(*p* 0.000) and COM+HA(*p* 0.000)
II-Central 3 ROI :Can not differentiated from ST (*p* 0.929) and COM+UA (*p* 0.357)
III-ROI of center :Can differentiated only from UA (*p* 0.000) and COM+UA (*p* 0.009)
B-In bone window
I-All nine ROI :Can only differentiated from UA(*p* 0.001) and COM+HA (*p* 0.000)
II-Central 3 ROI :Can differentiated from all others except COM(*p* 0.873)
III-ROI of center :Can not differentiated from COM (*p* 0.386) and COM(*p* 0.785)

Thus , pure UA can differentiated from struvite and COM in both tissue and bone window , and struvite can differentiated from other pure stones mainly on tissue window. Mixed COM +HA significantly differs from all other types (especially on all nine ROI and central 3 ROI while there was overlap when compare them on ROI of the center of the stone).

The mixed COM+UA and struvite +COM+HA stones are fall within intermediate CT number ranges between the lowest cut-off point (UA stone) and highest cut-off point (COM+HA stone),they can not significantly differentiated from pure COM and pure struvite and from each others .

The best absolute HU values for differentiation are those derived from the central three ROI and ROI of the center of the stones .Both of these were better at distinguishing different chemical compositions of calculi than the mean of the nine ROI.

CHAPTER FOUR

Discussion

Upper urinary tract calculi are a common problem in daily urological practice .Stone factors to be considered in the treatment of the kidney calculi include stone burden (size and number),stone composition ,and stone location . ESWL is now considered the treatment of choice for most of them (about 80% to 85% of simple renal calculi) . However , ESWL may not be a cost-effective option compared with other available treatments ,as , in some cases ,the optimum fragmentation of the stones is not possible even after three or four sessions , and an alternative treatment is required.

Stone fragmentation is difficult to assess prior to treatment . Thus there appears to be a need for a method which could help to predict stone fragility at the beginning of the treatment plan .

Choice of efficacious clinical management of symptomatic renal calculi can be facilitated by ascertaining the precise chemical composition of the calculus . None contrast spiral CT (NCSCT) is becoming a frequently used radiographic examination to establish the diagnosis and severity of calculus disease , and may be used to identify stone composition[6,13, 18,20,24,35,36].

Saw et al.[7] found that scanning stones that were smaller than the size of collimation subjected them to partial volume inaccuracies which had an impact on the measured HU values .They concluded that using a smaller collimation size permitted better accuracy in the prediction of stone composition .

In the present study ,we utilized a CT technique ,provided that it was clinically practical and would not require repeated imaging of the patients . The stones were scanned at 2 mm collimation . In other in vitro studies , 1 mm [6], 1.25 mm [37], 2 mm [20,36],and 5 mm[23] collimation were used . Using absolute HU values at 120 k V , we could differentiate pure UA (398-421) from all other types (in both tissue and bone windows), and pure struvite (642-1029) from pure COM (1128 -1280)(in tissue window). Mixed COM+HA(1456 -1568) had higher density and can differentiated from other types (in tissue and bone windows).Other mixed stones (struvite+COM+HA and COM+UA) could not differentiated from the pure struvite and pure COM) and from

each other .

Mitcheson et al.[36] report the same results for pure stones only ;they did not include mixed stones .Hillman et al.[23] could differentiate pure COM ,UA ,and struvite calculi using absolute HU values. Newhouse et al. [20] reported the results of scanning calculi including a mixed stones ; they could not distinguish calcium based and struvite stones from each other. Mostafavi et al.[6], using the absolute HU values at 120 k V ,could differentiate the three pure types.

Determination of stone composition by NCCT in clinical settings has also been reported[24,35].Nakada et al.[35] differentiated pure COM from pure UA using the absolute HU values ,while Motley et al [24] did not .

All these studies ,as well as the present study , showed the same trend from the least to the most dense calculi.

Table (11) shows the parameters and HU values for the above studies in comparison to the present study .The variations in absolute CT numbers may be attributed to the different scanners as well as the energy settings used .

Thus using of absolute HU values from either central three ROI ,or ROI of the center of the stone uncovered statistically significant differences among all pure stones but heterogeneity of most stones is a complicating factor that made the differentiation between the stones included with the intermediate group between highest cut-off point and lowest cut-off point so difficult .

Table (1):stones composed of calcium oxalate monohydrate determined by absolute HU values.

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	1398	1394	952	1079	1167	1388
2	521	709	1120	757	850	1320
3	1549	1541	1579	1193	1748	1816
4	1532	1867	1828	1632	1879	1837
5	1296	1127	892	1384	917	877
6	643	840	1085	892	991	1136
7	764	645	821	707	768	895
8	1745	1990	1679	1745	1643	1443
9	670	699	699	660	671	692
10	1219	1392	1389	1488	1453	1442
11	1327	1267	1625	1359	1517	1529

Table (1)

No.	Tissue window			Bone window		
	All nine	Central Three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
12	716	762	1616	1141	1199	1616
13	1059	1377	1286	1218	1238	1281
14	1274	1798	1461	1438	1433	1474
15	1199	1159	1168	1358	1236	1373

Table (2):Stone composed of uric acid determined by absolute HU values

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	105	220	205	335	229	205
2	445	361	266	470	406	549
3	504	361	542	423	406	542
4	331	376	388	304	385	319
5	785	709	584	987	780	592
6	34	32	35	45	47	53
7	432	425	430	427	425	435
8	570	640	626	638	768	757
9	264	340	523	396	572	545
10	469	500	443	419	550	567
11	613	653	692	568	591	581

Table (2)

No.	Tissue window			Bone window		
	All nine	Central Three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
12	440	548	559	552	465	402
13	281	331	232	379	405	429
14	303	360	367	330	356	353

Table (3):Stone composed of COM +UA determined by absolute HU values

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	481	341	451	419	299	462
2	1368	968	962	1337	643	1044
3	849	1007	1050	921	1161	1050
4	329	380	590	620	661	659

Table (4):Stone composed of Struvite +COM+ HA determined by absolute HU values

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	616	860	1320	830	1240	1450
2	806	1135	1389	1294	1413	1442
3	560	792	1336	673	1054	1373
4	620	761	1250	860	1210	1390
5	555	820	1321	770	1150	1395

Table (5):Stone composed of magnesium ammonium phosphate hexahydrate (Struvite) determined by absolute HU values

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	627	907	1160	732	774	1322
2	760	692	702	885	837	707
3	586	804	1155	1016	1010	1310
4	528	811	1110	950	1008	1210
5	710	720	1020	740	822	1310

Table (6):Stone composed of COM + HA (hydroxyapatite) determined by absolute HU values

No.	Tissue window			Bone window		
	All nine	Central three ROI	ROI of stone center	All nine	Central Three ROI	ROI of stone center
1	1303	1995	1980	1907	1697	1367
2	1524	1666	1702	1538	1600	1511
3	1343	1649	138	1522	1565	1378
4	1228	1705	1659	1611	1683	1654
5	1490	1082	1671	1538	1289	1656
6	1649	1650	1722	1635	1793	1458
7	1684	1229	1322	1539	1074	1595

Table (7) Absolute HU values of stones at 120 k V.

Type	n	Tissue window			Bone window		
		All nine ROI	Central Three ROI	ROI of the Stone center	All nine ROI	Central three ROI	ROI of the Stone center
Pure UA	14	398 ± 198	418 ± 181	421 ± 185	448 ± 210	460 ± 201	452 ± 180
Pure COM	15	1128 ± 380	1238 ± 444	1280 ± 349	1203 ± 333	1247 ± 364	1341 ± 328
Pure struvite	5	642 ± 93	787 ± 85	1029 ± 192	865 ± 126	890 ± 111	1172 ± 264
COM + HA	7	1460 ± 175	1568 ± 310	1456 ± 612	1613 ± 137	1529 ± 256	1517 ± 122
COM + UA	4	757 ± 462	674 ± 363	763 ± 288	824 ± 399	691 ± 355	803 ± 292
COM+HA+struvite	5	631 ± 102	874 ± 150	1323 ± 50	885 ± 239	1213 ± 132	1410 ± 34

Table (8) :Stone determination by absolute HU values of the stone center ROI at 120 kv .The p values for the independent sample t –test are given . p <0.05 indicates a significant difference .

		Tissue window					
		UA	COM	Struvite	Com+HA	COM+UA	COM+HA+Struvite
Bone window	UA		.000**	.000**	.000**	.061**	.000**
	COM	.000**		.040**	.387*	.001**	.904*
	Struvite	.000**	.471*		.097*	.038**	.410*
	COM+HA	.000**	.077*	.005**		.000**	.256*
	COM+UA	.022**	.004**	.248*	.001**		.009**
	COM+HA+Struvite	.000**	.386*	.040**	.785*	.001**	

* = Non Significant difference (P > 0.05)
** = Significant difference (P < 0.05)

Table (9) :Stone determination by absolute HU values of all nine ROI at 120 kv .The p values for the independent sample t –test are given . p <0.05 indicates a significant difference .

		Tissue window					
		UA	COM	Struvite	Com+HA	COM+UA	COM+HA+Struvite
Bone window	UA		.000**	.172*	.000**	.047**	.197*
	COM	.000**		.000**	.041**	.004**	.000**
	Struvite	.001**	.063*		.000**	.554*	.176*
	COM+HA	.000**	.000**	.000**		.000**	.000**
	COM+UA	.007**	.049**	.318*	.000**		.291*
	COM+HA+Struvite	.001**	.086*	.159*	.000**	.480*	

* = Non Significant difference (P > 0.05)
** = Significant difference (P < 0.05)

Table (10) :Stone determination by absolute HU values of the stone central three ROI at 120 kv .The p values for the independent sample t –test are given . p <0.05 indicates a significant difference .

		Tissue window					
		UA	COM	Struvite	Com+HA	COM+UA	COM+HA+Struvite
Bone window	UA		.000**	.037**	.000**	.206*	.009**
	COM	.000**		.003**	.019**	.001**	.016**
	Struvite	.003**	.024**		.000**	.276*	.929*
	COM+HA	.000**	.033**	.000**		.000**	.000**
	COM+UA	.105*	.001**	.628*	.000**		.357*
	COM+HA+Struvite	.000**	.873*	.024**	.042**	.008**	

* = Non Significant difference (P > 0.05)
** = Significant difference (P < 0.05)

Table (11) : Review of studies .

	Mitcheson et al .in vitro [22]	Newhouse et al. in vitro [27]	Hillman et al.in vitro [18]	Mostafavi et al. in vitro [1]	Nakada et al .in vivo[8]	Motley et al . in vivo ([25]	Sheir et al . in vitro [51]		Present study.in vitro	
CT scanner	Siemens somatom+2	EMI 7070	GE 8800	GE Hispeed	GE Hispeed	GE Hispeed	GE Light speed		Siemens Somatom+4	
Energy Setting	460 m A at 125k V 747 m A at 77 k V	90 m A at 120 k V	100m A at 80,120 k V	240 m A at 120 k V	200 m A at 120 k V	200 m A at 120 k V	240 m A at 120 k V		200m A at 120 k V	
collimation	2 mm	2 mm	5 mm	1 mm	3-5 mm	5 mm	1.25 mm		2 mm	
Surrounding Media	water	water	water	air	In patient	In patient	water		Air	
Absolute HU values							Tissue window	Bone window	Tissue window	Bone window
UA	540 ± 107	426 ± 51	448 ± 108	409 ± 118	344 ± 152	270 ± 134	548 ± 348	695 ± 376	418 ± 181	460 ± 201
Struvite	651 ± 108	715 ± 118	943 ± 259	666 ± 87	NA	401 ± 198	804 ± 364	1008 ± 381	787 ± 85	890 ± 111
Calcium oxalate	> 1,023	948 ± 67	1,273 ± 193	1,620 ± 232	652 ± 490	440 ± 262	809 ± 288	1130 ± 413	1238 ± 444	1247 ± 364

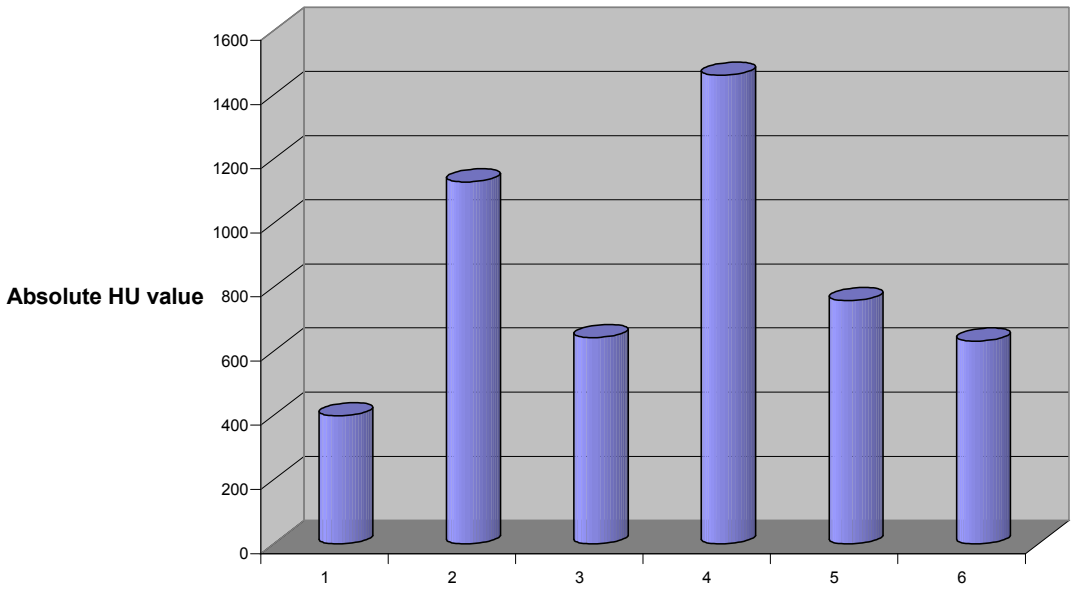

Figure (1) :The mean of absolute HU values of all nine ROI on tissue window
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvite

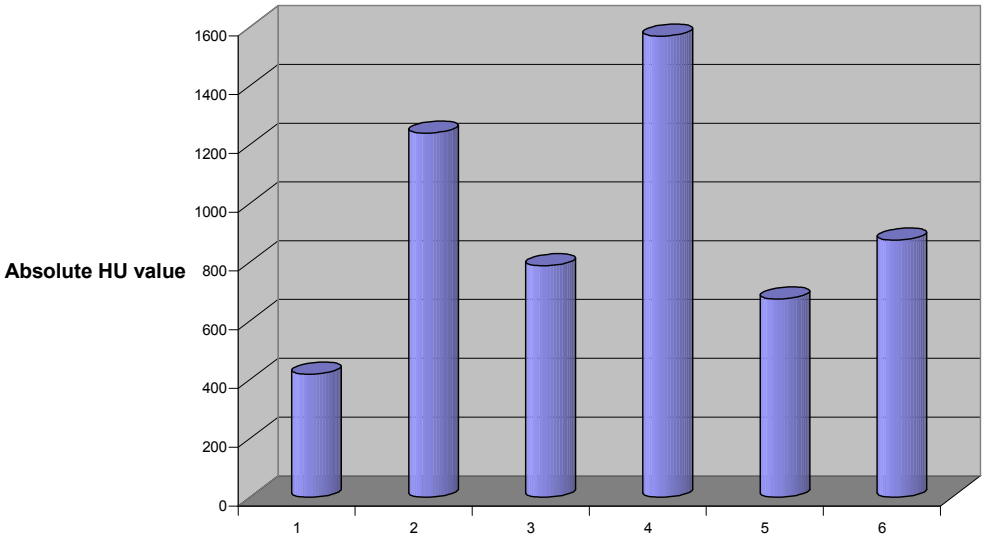

Figure (2) :The mean of absolute HU values of three center ROI on tissue window
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvit

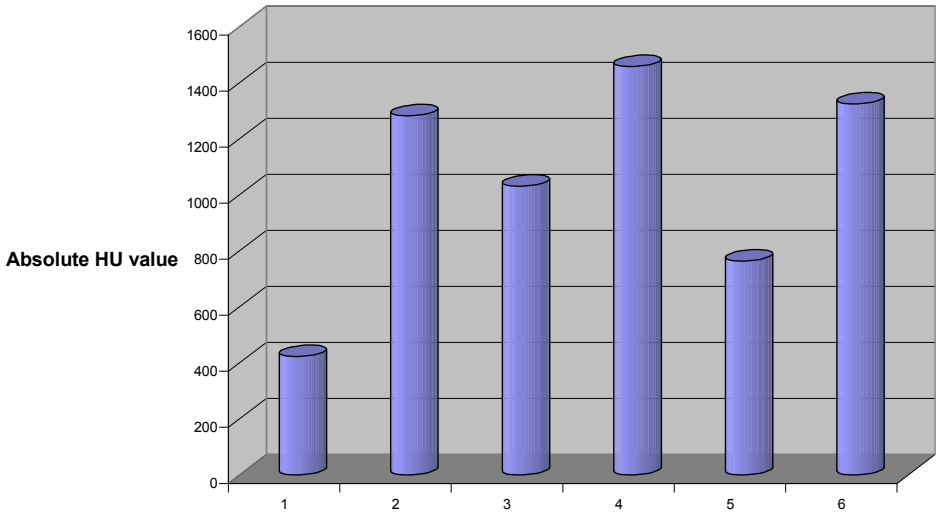

Figure (3) :The mean of absolute HU values of central ROI on tissue window.
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvite

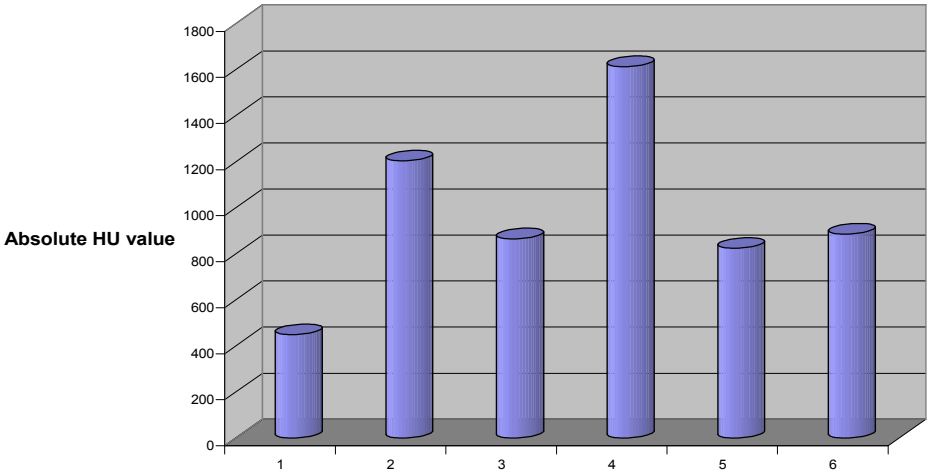

Figure (4) ;The mean of absolute HU values of all nine ROI on bone window.
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvite

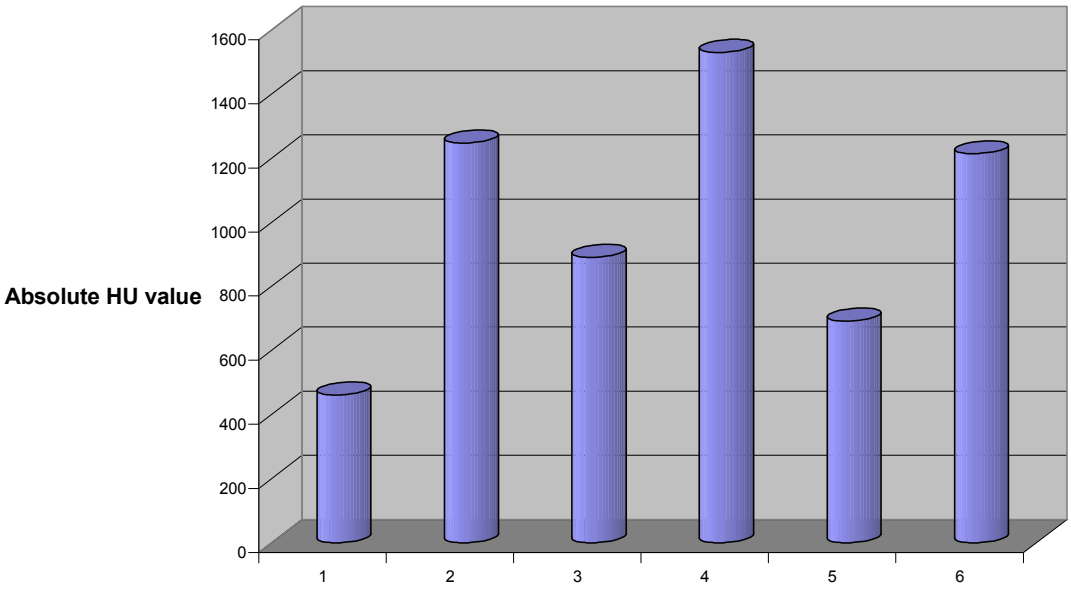

Figure (5) :The mean of absolute HU value of three central three ROI on bone window.
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvite

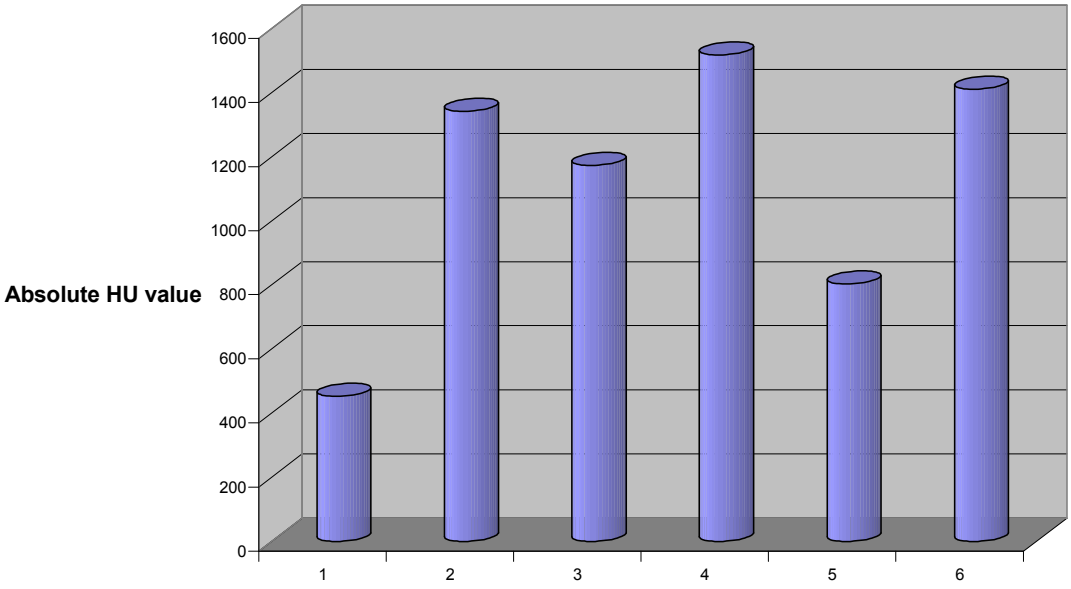

Figure (6) :The mean of absolute HU value of central ROI on bone window.
1=UA , 2=COM , 3=Struvite , 4=COM+HA , 5=COM+UA , 6=COM+HA+Struvite

CONCLUSION

1.In this study , we investigate fore correlation of CT number with calculus composition . It is unlikely that a radiological technique will produce a CT number that can provide a reliable and definitive substitute for laboratory calculus analysis .

2.A CT number may predict chemical composition of the stones , that the measurement of absolute HU values at a single energy level utilizing CT scanning with small collimation size can uncover significant differences among all pure stones and insignificant for mixed stones .

3.A CT number may give an indication , however , of the relative fragility and , therefore , fragment ability of a calculus .

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