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RESEARCH ARTICLE

STUDY ON IMPACT OF ANATOMICAL LOCATION OF HUMAN RENAL STONES ON MECHANISM OF NUCLEATION AND GROWTH IN SRI LANKAN POPULATION

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ABSTRACT

Urolithiasis is one of the major health issue in urinary system which causes large health care burden. Although many therapeutic options have been develop for the treatments of renal stones, mechanism of formation of renal stone is still remains as controversial. In order to detect formation of stone in different anatomical locations in renal system, we have examined 76 renal stone samples in different anatomical locations collected from Teaching Hospital, Peradeniya. Surface and cross sectional visual and microscopic analysis were done in all samples. Advanced morphological data and photographs were obtained through polarizing microscope using plane and crossed polarized light. Serial chemical characterization was carried out by using on X-ray Fluorescence (XRF) Spectrometer (Fisher-Scope XAN). From that study we found to have that the nucleation is the most important step for the formation of urinary calculi and it could be the organic matter. Also, the fragments of early formed stones within pelvicalyceal system could also be the nuclei of stones of other anatomical location. Nucleus and periphery have two different lamination patterns in polarized light and morphological and chemical data indicates significant difference between nucleus and periphery of a renal stone. It clearly shows that formation of nucleus and periphery of a stone is governed by two different processes. Based on these data urinary calculi can be differentiated according to their origin and growth. Also it may help to modify the correct treatment of urinary calculi.

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INTRODUCTION

Urolithiasis is defined as any calculi originate within urinary system which consists of kidneys, ureters, bladder and urethra and one of the most painful medical condition. Clinical history of renal calculi at initial stages may be asymptomatic in most of the cases but becomes symptomatic depending on the size, anatomical location and chemical composition (Kang *et al*., 2012; Kamoun *et al*., 1999). Though it does not directly associated with mortality, it may lead to frequent urinary tract infections, progressive deteriorating of renal functions and repeated painful hospital admissions causing large health burden to both the patient and health sector. Classification of renal stone is mainly based on their anatomical location and chemical composition (Grases *et al*., 2000).

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However, classifications based on external and internal morphological appearance of renal stones are rare although such categorization may give more information on the history of formation of renal stones (Grases *et al*., 2002). Though the formation of renal stone is a long term process and a multifactorial process, (Robertson, 2012) alteration of chemical composition and physical properties of urine are the most important factors for initiation stone formation (Lingeman *et al*., 1999). The formation of renal stone has multi step processes which include four stages; nucleation, crystal growth, crystal aggregation and crystal retention. The time needed for each process varies from individual patient (Basavaraj *et al*., 2007). Risk factors for renal stone formation can be classified as dietary, metabolic, environmental and urinary factors (Robertson, 2012). Prevalence of renal stones is increasing with the time across globally with male predomenence (Ramello *et al*., 2000; Robertson and Hughes, 1994; Scales *et al*., 2007). Rate of recurrence of renal calculi is also very high specially with calcium oxalate stones. For example, the recurrence rate of first-time stone formers in all kind of stones is approximately 40% in Germany (Siener *et al*., 2003). And without medical treatment the risk of stone recurrence in an individual patient is 40% within 3 years, 75% within 10 and 98% within 25years in England (Downey and Tolley, 2002). In Sri Lanka, though precise records are not available, nearly 3000 patients are having extra corporeal shockwave lithotripsy from the National Hospital, Colombo capital alone (Abeygunasekera, 2004). It is very important to identify the origin of renal stones in order to modify the treatments. Mechanism of formation initially described by Randall (Randall, 1936; Randall, 1937). Several authors have attempted to interpret the process of stone formation in humans and other animals (de Water *et al*,m 1999; Howard and Thomas, 1968). Though nucleation is the essential step of formation of renal stones, (Abeygunasekera, 2004) it is still controversial phenomenon. Due to the fact that binding of calcium to the urinary protein such as Tamm-Hors fall glycoprotein, there is possibility to formation of nucleus with the association of such proteins (Boyce *et al*., 1955). They have ability to induce calcification in vitro (Boyce *et al*., 1954) under certain conditions. However, the theory of the activating role of urinary proteins has been abandoned later despite it could not be disproven (Fleisch, 1978). Recent investigations suggested that homogenous nucleation that is formed from pure solution, plays a role to form nuclei (Finlayson, 1978).

Urine is not a pure solution and nucleation in urine often occurs over an existing surface, or an alternative structure and this process is known as heterogeneous nucleation (Fleisch, 1978). But latter, there is a high possibility for the formation of crystals on the surface of early formed nuclei. Therefore, secondary nucleation may result in the rapid production of crystals and this can be describe as Epitaxy, a process whereby material of one crystal type is precipitated upon the surface of another whose lattice dimensions are almost identical (Lonsdale, 1968). A study based on artificial urine, it was revealed that the possibility for the formation of calcium oxalate is higher than that of calcium phosphate (Grases and Llobera, 1998). Further, calcium oxalate is the commonest and important constituent for renal calculi (Downey and Tolley, 2002; Krishnamurthy *et al*., 2003) and approximately 85% of the stones are consisted of calcium oxalate associated with minor calcium phosphate although, phosphate salts are commonly found chemical constituents in urine. It indicates that precipitation of calcium oxalate is much favorable despite their lower concentrations (Grases *et al*., 2002; Abeygunasekera, 2004). So far, many studies have been carried out on morphological differentiation of renal stones based on chemical composition (Downey and Tolley, 2002). However; morphological differentiation with respect to the anatomical location, nucleation, lamination and crystal arrangements has not yet clearly been established. Despite, extensive studies have been performed related to occurrence of renal stone in many parts of the world in the recent past, only few investigations have been carried out in Sri Lanka (Chandrajith *et al*., 2006; Abeygunasekera *et al*., 2002). Out of these studies described the variation of chemical composition of renal stones with respect to the geographical location of the country and the other discussed on the incident rate of stag horn calculi. There are no any reported literature regarding the correlation of anatomical location and the morphological appearance even in other parts of the world. However, it can be assumed that there should be a strong relationship between the morphological features of stones (both external and internal) and anatomical locations due to different environments of these locations. Therefore, correlation of such data is useful to interpret the origin and growth of stones. Thus, present study is focused to characterize the kidney stones with respect to the anatomical locations and chemical composition. Further it is aimed to assess the nucleation and the rate of growth of kidney stones at different anatomical locations.

MATERIALS AND METHODS

Ethical approval for the study was obtained from the Ethical Review Committee of Faculty of Medicine, Peradeniya. Sample collection was carried out from patients who underwent open surgeries due to renal stone disease, irrespective of their age, sex and ethnicity after obtaining their written consent in Teaching Hospital, Peradeniya, Sri Lanka. Samples were collected soon after the surgical removal in to clean screw capped glass bottles. They were sealed until the analyses were performed. Seventy six (76) samples were collected from March 2013 to December 2013. Samples were cleaned first with surgical spirit in order to remove blood and body fluid followed by distilled water and deionized water. Then they were dried in an oven at 70°C for 60 minutes and weight was recorded. Samples were sealed in plastic bags until the analyses were performed.

Analyses include basic petrographic studies, including visual estimation of grain size, shape, appearance of surface, availability of crystals on the surface. The outer surface of stones was observed using optical stereoscopic microscope. Then the stones were cut by Fred's saw perpendicularly to the surface and the nucleus and the periphery zones of the stones were selected for most of sections. Microscopic studies were carried out to assess the size of crystals and to interpret the abundances and nature of amorphous materials, internal textural characteristics and the porosity of stones at the Department of Geology, University of Peradeniya. Petro graphic findings were confirmed by the chemical analysis carried out on X-ray Fluorescence (XRF) Spectrometer (Fisher-Scope XAN) at the Department of Physics, University of Peradeniya. A series of point analysis were carried out and average values were recorded. XRF analysis was performed from the nucleus area to periphery zones in order to compare the chemical and mineralogical variation within the specimen and to find out any variation based on the samples collected from different anatomical locations. Analytical error of the XRF Spectrometer is 15 to 20% without standards while it is 5% with standards.

RESULTS AND DISCUSSION

Colour Variation and Intensity of Cavitations

Visual observations of renal stones from three main different anatomical locations show that colour of them varies widely from pure white to dark brown depending on the conditions

Table 01. Average values of relative abundance of elements in the studied kidney stones. The percentages are given with respect to the all measured elements and not with total composition

Element	Nucleus area (%)	Peripheral area (%)
Ca	77.252	75.6
P	13.082	10.4625
Co	0.017	0
Cr	2.411	3.06
Fe	0.032	0
S	5.988	9.78
K	1.202	1.1875

prevailed at their locality. Most of the stones recovered from bladder are lighter coloured ranging from white to corn yellow. Ureteric stones are much darker in colour usually dark brown while stones from pelvicalyceal system show medium dark orange in colour. Cavitations of renal stone also shows a significant variation. Staghorn calculi show the highest percentage of cavitations (about 10%) and the pelvicalyceal system has the next higher percentage of cavitations. Ureteric stones have lesser amounts of cavitations and the lowest percentage of cavitations is recorded from bladder stones.

Morphological Characteristics

Surface of renal stones ranges from smooth to jagged in nature and overall shape of them varies from spherical to irregular in shape. The shape of the renal stone is greatly influenced by their anatomical location. Ureteric stones are spherical in shape which must be due to the fact that they in a hollow tube. However, bladder stones are oval in shape due to their free movements within the bladder. Stones developed within the kidney are irregular in shape and usually acquire the shape of hollow space of pelvicalyceal system. Ureteric stones are characterized by smooth surfaces except at the growing end, while bladder stones are jagged in nature. Stones from pelvicalyceal system and from the kidney show jagged and spiky surfaces. Spiky surfaces are mostly found from growing end in both ureteric and kidney stones. Growing end is defined as the surface which face against the urine flow and such situations can be found only within kidney and ureter. Size of stone also shows a significant variation ranges from 10mg to 137.81g. Smaller size stones are abundant in ureter and largest one was recovered from bladder.

Nucleation, Crystallinity and Laminations

Nucleus of renal stone is mainly consists of brown - black substances with irregular shapes. The brown, black substances are mainly free of crystals. So they are not sensitive to the depolarized light. Substances which contained high amount of organic matter have this feature. It indicates that nucleus of renal stone is mainly consist of organic matter rather than inorganic crystals. Nucleus of renal stones recovered from bladder and ureter was different and it had a higher degree of crystals and lesser amount of organic matters. They are already having series of fragmented laminations in the nucleus. It implies that nucleus of these stones has formed from other sites of renal system and migrated to these places. They are very similar to cross sections of renal stones recovered from pelvicalyceal system. Microscopic observations revealed some

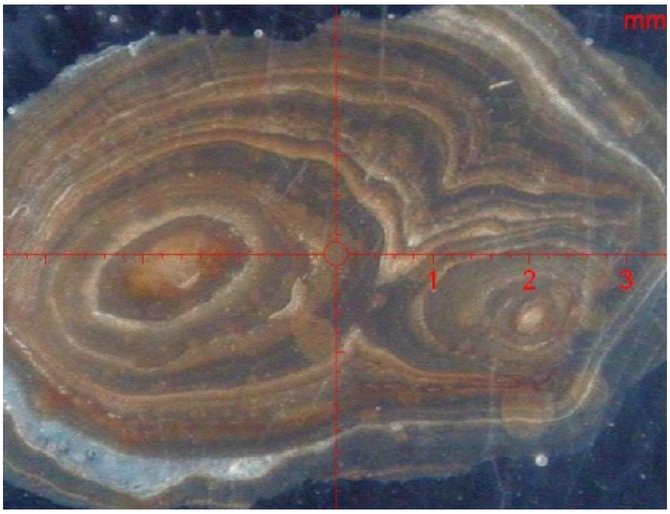


Figure 1. Stereoscopic microphotograph of separately grown nuclei in staghorn calculi

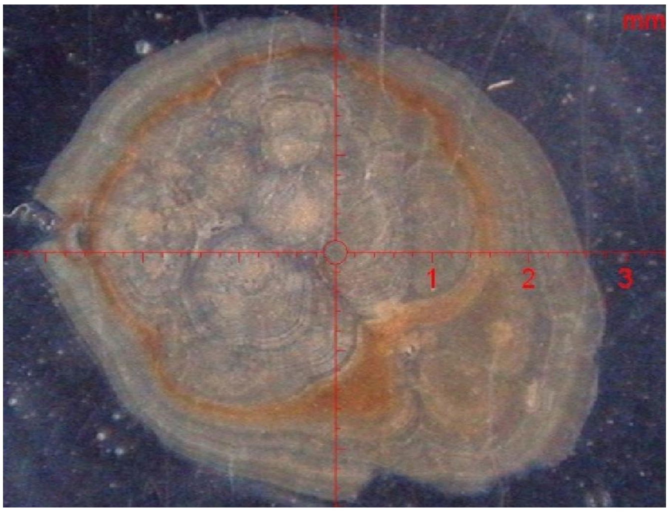


Figure 2. Stereoscopic microphotograph of cluster of nuclei developed simultaneously which later formed composite nucleus

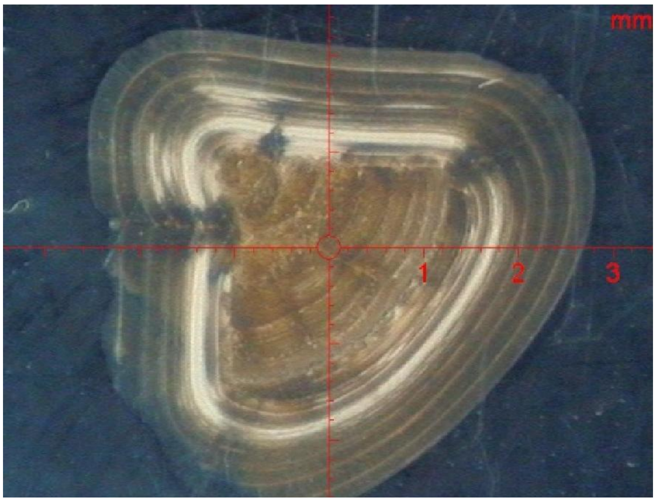
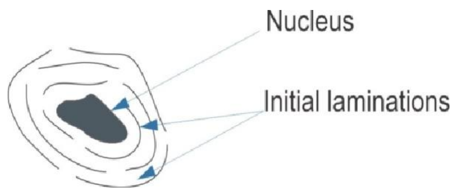


Figure 3. Microphotograph of a nucleus which was a fragment of previous stone from ureteric calculi

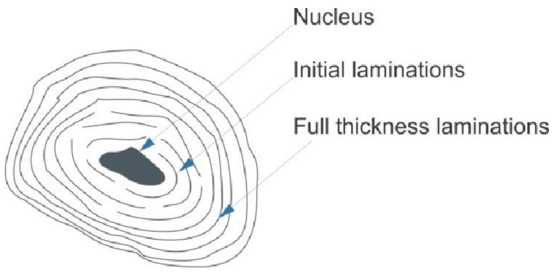
distinctive lamination patterns from the stones of different anatomical locations. Renal stone had unique pattern of

First lamination series



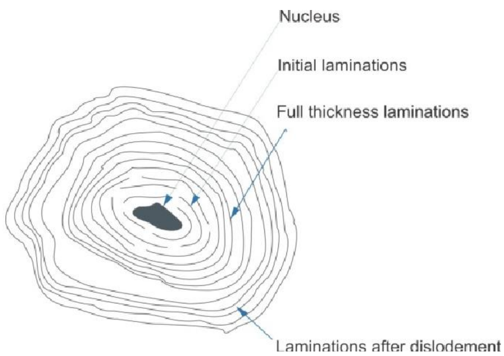
Initial discontinued irregular laminations occurring around the nucleus which is mainly consist of organic materials.

Initial full thickness laminations



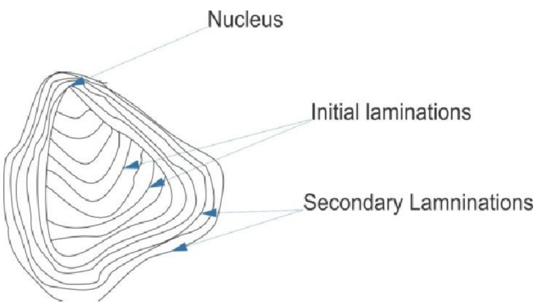
Initial full thickness laminations occurring surrounding the initial irregular laminations. Line thickness is almost the same. That implies initial both laminations are occurs in same environmental conditions.

After dislodgement, secondary laminations



Series of secondary full thickness laminations occurs after 1st full series of laminations. But line thickness difference indicates that formation of lamination occurs in two different environments.

Bladder calculi formed after Extracorporeal Shock Wave Lithotripsy (ESWL)



The second stage of laminations has been taken place around the fragment of preexisting calculi and thicknesses of these are different from that initial lamina.

laminations fallowing the formation of nucleus. Lacking of laminations in nucleus area indicates that the nucleation of renal stone was not a sedimentation process. The microscopic studies show that formation of concentric laminations starts after the completion of initial nucleation. In the areas of nuclei, crystalline materials are rare and they are mostly amorphous in nature. If the stone has more than one nucleus, each nucleus is individually laminated and occurs as composite areas. (see Fig. 1) Out of the studied samples composite nuclei are not common and their percentage is less than <25%.(see Fig. 2) The nuclei of renal stones extracted within kidney are asymmetric and they are located closer to the periphery zones whereas nuclei of all the other stones are mostly in the central location. The darker appearance and the amorphous nature of nuclei are mostly organic as shown in the literature. Laminations around the nuclei are usually interrupted by amorphous organic matrix and are limited to narrow coatings. (see Fig. 1) The crystallinity of such areas are relatively low (mostly micro-crystalline) compared to the laminations of the peripheral areas of the stones. The outer part of the nucleation region is marked by a thin layer of organic origin and it is mostly dark brown in colour. Regular circular laminations were observed after this zone. Tightly arranged well crystalline columnar crystals are attached to the organic rich matrix. The crystals are mostly elongated and the size of crystals gradually increases towards the outer part of the stone. The available organic matrix and the cavitations are relatively low compared to the inner part. After development of initial regular circular laminations around the nucleus, sudden disruption of the lamination pattern was observed and new generation of laminations were noted. Such pattern covers the entire nuclei and it is independent from earlier laminations with different textural characteristics. Interestingly, stag horn calculi do not show both laminations described above. However ureter and bladder calculi shows well developed secondary laminations after the initial regular lamination series. Small renal calculi found within the kidney also show the same pattern. Bladder calculi which grow on fragments formed by extra corporal shock wave lithotripsy (ESWL) have similar pattern but they are lacking of primary regular crystalline laminations because their nuclei are the fragmented calculi. Further, presence of large crystals with clear surfaces show that the rate of crystallinity and growth of bladder stone is much higher than those found in other two locations. Ureteric stones are usually darker in colour under plane polarized light and, their crystallinity and rate of growth are much lower. Ureteric stones frequently interact with ureteric wall which causes the haematurea. Therefore, the darker colour of them may be due to accumulation of iron derived from haemoglobin.

Factors Influencing the Characteristics of Renal Stones

Colour of a stone is mainly determined by the chemical composition of urine. However present study revealed that their anatomical location also plays the major role on the variation of the colour. The rate of crystallinity, extent of incorporation of organic matters and growth rate are variable in different locations and it was resulted from the colour variation. The microscopic observations revealed that higher percentages of cavities are enriched in darker nuclei areas of stones recovered from pelvicalyceal system, specially in stag horn calculi. Amorphous areas which supposed to be rich in organic matter are normally high in stag horn calculi. The lowest amounts of organic matter were noted from bladder stones and their cavity content is remarkably low. Therefore, it can be assumed that the major factor that effect on the cavitations of a stones is their organic content. Cavitations are not significant in the periphery areas, predominantly in ureteric stones and bladder stones. It indicates that organic matters do not attach to stones during the latter period of the stone growth and only the inorganic processes are dominated. Presence of cavitations is an essential criteria for ESWL (extra corporal shock wave lithotripsy). Higher percentage of cavity helps to easy fragmentation of a stone. Stones located in pelvicalyceal system are the most potent candidates for the ESWL while bladder stones are having lowest therapeutic outcome. Presence of cavity or presence of amorphous organic matter in a stone determines its therapeutic outcome (Pishchalnikov *et al*., 2003; Zhong *et al*., 1997; Zhong and Preminger, 1994).

Chemical Characteristics

The variation of elemental composition within the stones was determined by spot analysis from nucleus to the peripheral area. Calcium is the most abundant cation in all regions and several elements were detected in the nucleus area compared to the peripheral area of each stones (see the Table 01). The values of magnesium are not considered since the analytical error for the Mg is high. It is very clear that higher variation of elements in nuclear area of renal stone is indicates that formation of renal stone is complex process and involves large number of compounds. But after formation of nucleus, peripheral area shows limited variation in chemistry. These significant variations of chemical composition in two zones indicate that formations of these zones are governed by two different chemical processes. Results of petrologic study are also conformed the observation. Further, it can be suggested that nuclear formation is predominantly an organic process and peripheral zone formation is predominantly an inorganic process.

Conclusion

Present study revealed that formation of nuclei is taken place at higher in pelvicalyceal system. After the maturation of nuclei, the stone is dislodged from the site of formation, and further develops as a renal stone in other anatomical locations within urinary system. However, the causes for the formation and dislodgement are yet to be identified. Further, it was noticed that the nucleation is the most important step for the formation of renal stones and it could be the organic matter. Also, the fragments of early formed stones within pelvicalyceal system could also be the nuclei of stones of other anatomical location. Initial nuclear formation is taken place at higher in pelvicalyceal system the extent of crystallization and the organic matrix as well as percentage of cavities might be important to establish the right treatment in pharmacological or with extracorporeal shock wave lithotripsy (ESWL).

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Conflict of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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