A retrospective chart review of the demographics of patients presenting with urinary calculi to Inkosi Albert Luthuli Central Hospital Urology Department over a 2-year period

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As the candidate's supervisor I have approved this thesis for submission.

Supervisor

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Date: 26-05-2022

Declaration

I, Dhesigan Naidoo....., declare that:

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Dedication

I dedicate this thesis to my parents for guiding me through my medical education and to my wife and children for their support during my fellowship training and research.

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Abbreviations

DASH	Dietary Approaches to Stop Hypertension
IALCH	Inkosi Albert Luthuli Central Hospital
IQR	Interquartile range
uOR	Unadjusted odds ratio
aOR	Adjusted odds ratio
95%CI	95% Confidence interval

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Abstract

Racial differences in the characteristics of urinary calculi are poorly described in the South African context, limiting our local understanding of urolithiasis pathology, and thwarting our efforts in designing appropriate preventative interventions. We sought to investigate differences in urinary calculi characteristics amongst the main racial groups in KwaZulu-Natal, South Africa.

We conducted a retrospective chart review of patients with urinary calculi at a quaternary hospital in KwaZulu-Natal, South Africa during 2018-2019. We collected data on the patient's age, sex, race (Caucasian, Asian, Black African), residence, and pre-ureteric stenting. Five study outcomes were investigated across racial groups: number of calculi, location of the calculi, size of the calculi, density of the calculi (Hounsfield Unit measurement >600), and the number of operative interventions performed. Data was analysed with descriptive statistics, the chi-squared test, and unadjusted/adjusted logistic regression. Our study sample consisted of 147 patients (10.9% Caucasian, 55.8% Asian, 33.3% Black African). Most patients (86.4%) were from urban areas. A higher proportion of Black Africans had urinary calculi with Hounsfield Unit measurements >600 (p=0.002). In the logistic regression models, Black Africans had a higher probability of having urinary calculi with Hounsfield Unit measurements >600 (Unadjusted Odds Ratio: 7.17, 95% Confidence Interval: 2.00-27.80; Adjusted Odds Ratio: 18.75, 95% Confidence Interval: 3.37-157.57).

Our analysis suggests that Black Africans are at higher risk of having harder urinary calculi than other race groups. This has implications for urolithiasis management and highlights the importance of primary prevention in this group. We recommend additional research to confirm our findings.

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Part 1: Literature review

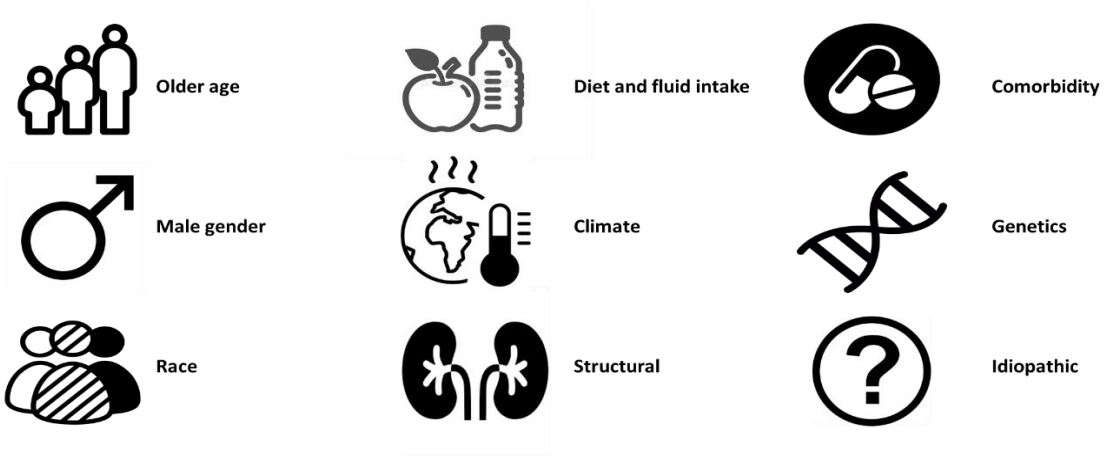
Definition and epidemiology of urinary calculi:

Urinary calculi are mineral concretions which form in the urinary system and are common worldwide. Estimates of disease prevalence from the United States range between 7.1-10.6%, with 5.9-9.2% of Americans reporting having passed at least one urinary calculus during their lives (1). Prevalence rates of urinary calculi in Asian countries range between 6% and 12% (2), while in Europe the prevalence of urinary calculi ranges between 5% and 15% (3, 4). Prevalence studies in African countries are rare. Lang et al., estimated that there were 77.8 million incident cases of urinary calculi worldwide in 1990 versus 115.6 million incident cases in 2019 (5). Laing et al., also found that urinary calculi were most common amongst those individuals aged 55-64, and that males were more affected by this condition than females (5).

A list of some of the most important risk factors for urinary calculi are presented in Figure 1. An analysis of data from the United States National Health and Nutrition Examination Survey showed that age groups >40 years had a two- to five-fold higher odds of urinary calculi when compared with 20-39 years olds (6). A possible explanation for the association between increasing age and urinary calculi might be the duration of exposure to other important risk factors for calculi development (7). Individuals who are older would have a longer exposure to these risk factors and higher risk of calculus development than younger individuals. The preponderance of urinary calculi amongst males has traditionally been attributed to the higher burden of risk factors in this group when compared with females (8). Although urinary calculi are still more common in males than females, the risk factor burden has increased amongst

females in recent decades. This has led to a corresponding decrease in the male-to-female ratio of disease (8).

Figure 1. Important risk factors for urinary calculi



Large American studies have demonstrated racial differences in the risk for urinary calculi. Data from The Southern Community Cohort Study suggests that the risk of urinary calculi is almost twice as high in Caucasians when compared with African Americans (9). Similarly, data from the United States National Health and Nutrition Examination Survey also shows that the odds of developing urinary calculi in non-Caucasians is up to 75% lower than that of Caucasians (6). It has been proposed that the differences in risk of urinary calculi between Caucasians and persons of African ancestry might be due to higher levels of protein-based stone inhibitors, a lower mean urinary calcium, and a lower prevalence of hypercalciuria (9). A South African study by Lewandowski et al., found that when compared with Caucasians, Black Africans did not have increases in urinary oxalate when placed on a high oxalate, low calcium diet. It was subsequently proposed that there are racial differences in the renal handling of dietary calcium and oxalate which might explain why urinary calculi have traditionally been considered rare in Black Africans (10, 11). This narrative does appear to be changing, in alignment with the changing dietary habits in those of African ancestry (12).

Other comorbid diseases such as obesity, diabetes, hypertension, metabolic syndrome, and gout are associated with urinary calculi. In an analysis of data from three large prospective cohorts, Taylor et al., reported that the risk of urinary calculi was 33% higher in obese men when compared with non-obese men (13). In the same analysis, the risk of urinary calculi was found to be 90% higher in obese women when compared with non-obese women (13). When compared with non-obese individuals with urinary calculi, obese individuals with urinary calculi have a lower urine pH, hyperuricosuria, hypercalciuria, and hypocitraturia – all of which are important biochemical contributors to urinary calculi development. In addition, obesity is linked to the development of insulin resistance and diabetes, which are also risk factors for urinary calculi (14).

Hypertension being a definite risk factor for urinary calculi is much weaker than it is for diabetes (15). Nevertheless, analyses of data from large, prospective cohorts in the United States have reported an association between a history of nephrolithiasis and subsequent hypertension, hinting that there might be common, unknown pathophysiological mechanisms involved in the development of both conditions (16, 17). A recent meta-analysis of observational studies by Roughley et al., reported that the presence of gout was associated with a 77% higher probability of urinary calculi, however the exact pathophysiological mechanism underlying this association is still poorly understood (18).

Metabolic syndrome (the presence of any three of the following comorbidities or biochemical characteristics - central obesity, low high-density lipoprotein, hypertriglyceridemia, hypertension, and elevated fasting glucose) has a wide-range of long-term complications, including an up to 2-fold higher risk of urinary stone disease (19, 20). The underlying mechanism through which metabolic syndrome confers a higher risk of urinary calculi is

similar to that proposed for obesity and diabetes – uric acid and calcium oxalate crystal formation (19).

A recent meta-analysis by Lin et al., summarized the overall impact of various dietary interventions for prevention of urinary stones. Intake of fruits, vegetables and fiber were found to be protective against urinary stones, while meat intake was found to have a harmful effect (21). Furthermore, a DASH-style diet, dietary magnesium, dietary potassium, dietary calcium, and caffeine were found to have a protective effect. Fructose and dietary sodium were found to have a harmful effect (21). Findings for dietary vitamin supplementation were inconclusive. Increased fluid intake, alcohol, tea, coffee, water, and beer were protective against urinary stone formation. On the other hand, carbonated cooldrinks containing fructose consumption was found to be associated with a higher risk of urinary stone formation (21).

Climate change is set to have an important impact on human health in the years to come. Rates of urolithiasis are already reported to be increasing in regions where mean temperatures are higher, probably due to the to the impact of hot temperatures on fluid status and urine volume (22).

Underlying genetic mechanisms of are usually insufficient on their own to cause urinary calculi. It is proposed that multiple genes are involved in this process, and the interaction of these genes with various dietary and environmental factors gives rise to urinary calculi (23). There have been several genes identified in recent years which are thought to impact the functioning of key enzymes, transporter/exchange proteins, and receptors in the kidney that are involved in preventing crystal formation. Genetic polymorphisms can impair the function of these key enzymes and proteins, thereby facilitating crystal formation (23).

Horseshoe kidney and medullary sponge kidney are two important anatomical factors which contribute to the formation of urinary calculi. Horseshoe kidney (renal fusion) is amongst the most commonly reported congenital disorders and can lead to ureteric obstruction in almost one-third of cases (24). The impaired drainage of urine from the ureteric obstruction in a horseshoe kidney can lead to urinary stone formation (24).

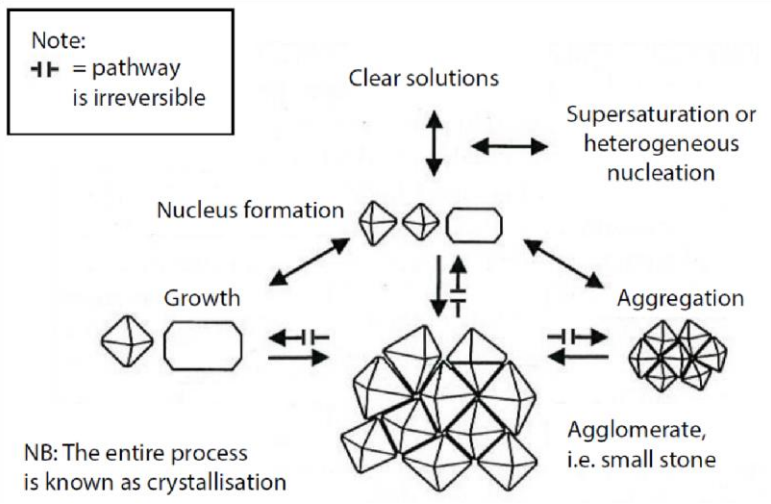
Medullary sponge kidney is a less common condition and may arise through congenital or genetic mechanisms (25). Nephrocalcinosis, hypercalciuria and hypocitraturia are commonly observed in this condition. It explains the high frequency of urolithiasis in patients with medullary sponge kidney (25).

Idiopathic hypercalciuria is common in urolithiasis and is defined as an excess urine calcium excretion without an apparent underlying cause. It may result from alterations in calcium metabolism in the gut, bone, the kidney alone, or in all three of these sites (26). This culminates in excessive urine calcium excretion and promotes urinary stone formation (26).

Mechanism of urinary calculus development:

The formation of urinary stones is a complex process and has been summarized in a recent review paper by Meyers and Naicker (27). As per Figure 2 (27), the first step is crystal nucleation, which involves the initial "sticking together" of crystal nuclei. Crystal nucleation is highly dependent on the composition and concentration of urinary solutes. The next step involves crystal growth, as more nuclei aggregate around the initial crystalline structure. Subsequently, a small urinary stone is formed, also known as an agglomerate. This initially small urinary stone might then increase in size as more crystal structures aggregate and stick together.

Figure 2. Process of urinary stone formation



Impact of urinary calculi on mortality, morbidity, and health expenditure:

Urinary calculus associated death, although rare, has seen an increase in the past few decades (28). A systematic review by Whitehurst et al., reported 2550 deaths from urinary stones in the literature between 1999 and 2017 (28). The majority of these deaths (78.0%) were associated with multiple interventions and other non-specific stone related mortality. Almost 20% of stone-related mortalities occurred following percutaneous nephrolithotomy (28). A recent analysis of surgical patient data from Australia reported that 9.7% of urological deaths were related to urinary stones (29). The most common cause of death reported was secondary sepsis, which was responsible for nearly half of deaths in patients being surgically managed for urinary stone disease (29). Of note, these reports do not account for patients who develop chronic kidney disease (CKD) and demise due to CKD (limited access to renal replacement therapy in Africa further contributes to these deaths)

Morbidity from urinary stones usually involves pain secondary to renal colic, haematuria and/or infection (30). However, urinary stones might also be a contributing factor to end-stage renal disease. Recurrent urinary stones are particularly concerning. An analysis of

nearly 7000 patients from Olmsted County in the United States (1984-2012) found that stone disease was associated with a 2-fold and 4-fold higher risk of end-stage renal disease in symptomatic and asymptomatic patients, respectively (31). Similarly, a large Canadian cohort study also reported a two-fold higher risk of end-stage renal disease in patients who reported one or more stone episodes versus those who had no episodes of urinary stones (32). A nationwide study from Taiwan reported that the adjusted risk of chronic kidney disease was two-times higher in patients who had urinary stones versus those who did not (33). The incidence of chronic kidney disease in the urinary stone group was 11%, and significantly higher than the control group in this study (33).

The impact of urinary stones on patient quality of life was summarized in a systematic review of the published literature conducted by New and Somani (34). The authors reported that lower overall quality of life was a consistent finding for most papers included in their systematic review (34). Regarding the specific domains of the various quality of life questionnaires, patients with urinary stones reported lower pain and general health scores when compared with their comparator groups. Another important finding from the review was the between stone episodes and quality of life, which appears to improve with the passage of time (34). Interestingly, the bulk of the published literature suggests that surgical intervention has a negative impact on quality of life in patients with urinary stones (34). This might be due to the complications associated with surgical intervention for urinary stones.

The healthcare costs associated with urinary stones can be substantial. Although there is very little economic data available from lower-income countries, economic data from the United States suggests that the healthcare costs attributed to urinary stone disease amount to $2 billion each year (35). The indirect costs of urinary stone disease must also be taken into

account, as this condition affects persons of working-age. Urinary stone disease is a painful condition, and patients might be unable to work or might require time away from work to undergo surgical intervention and recover. An estimated one third of patients treated for urinary stone disease will miss work, which can have financial implications for the patient (36).

Diagnosis and management of urinary calculi:

Diagnosis of urinary calculi entails clinically assessment and imaging of the urinary tract (37). The most frequently reported symptoms of urinary calculi include pain, haematuria, nausea, vomiting, and urinary tract infection. Often, laboratory test results will fall within the "normal range", unless there is concurrent urinary infection (37). Imaging modalities include plain film abdominal X-ray, ultrasound and non-contrast computed tomography scan, the latter being the gold standard for diagnosis (37). However, many patients will have a plain Xray and ultrasound as initial screening investigations at our referral centres before a non-contrast computed tomography is performed resulting in the high cost of diagnosis.

Management modalities for urinary calculi comprise conservative measures and surgical options. Small stones (<10mm in size) might be spontaneously passed by the patient, and conventionally the smaller and the more distal the stone, the quicker it will be passed by the patient (37). Medical expulsive therapy, by the administration of alpha-blockers or calcium channel blockers, can increase the successful passage of a urinary by approximately 50% (37).

Failed conservative management, (i.e., recurrent pain, nausea, vomiting and stone persistence) necessitates surgical intervention for removal of the urinary stone. Common surgical options employed are extracorporeal shockwave lithotripsy and ureteroscopy (38).

Ureteroscopy and extracorporeal shockwave lithotripsy are commonly used surgical methods by urologists (39). However, the effectiveness of ureteroscopy and extracorporeal shockwave lithotripsy is often dependent on the size of the urinary stone being removed. For larger stones, more invasive surgical approaches such as percutaneous nephrolithotomy (37). A summary of the pros and cons of the various surgical approaches for urinary stone management is provided in Table 1 (37).

Table 1. Pros and cons of the various surgical approaches to urinary stone management

Approach	**Pros**	**Cons**
Shockwave lithotripsy	Minimally invasive.	Lower stone free rates. Likely to require additional intervention. Possible risk of urinary obstruction when patient passes stone fragments.
Ureteroscopy	High stone-free rate. Can be performed on anticoagulated and pregnant patients.	Requires stenting. Patient at risk for ureteral injury.
Percutaneous nephrolithotomy	Highest stone-free rates for large renal stones	Bleeding risk. Potential risk of injury to surrounding structures.

The recurrence rate for urinary stones is approximately 50% (40). Therefore, lifestyle modification has an important role to play in urinary stone prevention. Low urine volume is the most common abnormality and the single most important factor which must be addressed to prevent urinary stone recurrence. Drinking sufficient water to prevent dehydration is therefore one of the more established preventative measures available to reduce the risk of

recurrent urinary stones (41). Diets low in salt and animal proteins are also helpful in decreasing the frequency of recurrent calcium oxalate stones (42).

Gap in our current understanding of urinary calculi:

Studies which have investigated racial differences in the characteristics of urinary calculi in the multiracial South African population are rare (43). The overall non-communicable risk factor burden has increased amongst Black South Africans since the fall of Apartheid (44), and it is possible that the importance of urinary calculi has increased in Black South Africans, who have previously been considered at lower risk for this condition when compared with the other racial groups (10, 43). This paucity in the knowledge also limits our local understanding of urolithiasis pathology and thwarts our efforts in designing appropriate preventative interventions for high-risk racial groups.

Study aim:

To investigate whether there are differences in the characteristics of urinary calculi amongst the three predominant racial groups in the Province of KwaZulu-Natal, South Africa.

Study objectives:

To retrospectively compare the following outcomes of interest amongst Black Africans, Caucasians, and Asians attending the urology unit of a quaternary hospital in Durban, South Africa for the management of urinary calculi:

- Number of calculi
- Location of the calculi
- Size of the calculi
- Density of the calculi

- The number of operative interventions performed

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Part 2: Submission-ready manuscript

(Currently under peer-review at "Journal of Renal and Hepatic Disorders")

Differences in urinary calculi characteristics amongst the three main racial groups in KwaZulu-Natal, South Africa

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Conflict of interest: None

Abstract

Racial differences in the characteristics of urinary calculi are poorly described in the South African context, limiting our local understanding of urolithiasis pathology and thwarting our efforts in designing appropriate preventative interventions. We sought to investigate differences in urinary calculi characteristics amongst the main racial groups in KwaZulu-Natal, South Africa. We conducted a retrospective chart review of patients with urinary calculi at a quaternary hospital in KwaZulu-Natal, South Africa during 2018-2019. We collected data on the patient's age, sex, race (Caucasian, Asian, Black African), residence, and pre-stenting. Five study outcomes were investigated across racial groups: number of calculi, location of the calculi, size of the calculi, density of the calculi (Hounsfield Unit measurement >600), and the number of operative interventions performed. Data was analysed with descriptive statistics, the chi-squared test, and unadjusted/adjusted logistic regression. Our study sample consisted of 147 patients (10.9% Caucasian, 55.8% Asian, 33.3% Black African). Most patients (86.4%) were from urban areas. A higher proportion of Black Africans had urinary calculi with Hounsfield Unit measurements >600 (p=0.002). In the logistic regression models, Black Africans had a higher probability of having urinary calculi with Hounsfield Unit measurements >600 (Unadjusted Odds Ratio: 7.17, 95% Confidence Interval: 2.00-27.80; Adjusted Odds Ratio: 18.75, 95% Confidence Interval: 3.37-157.57). Our analysis suggests that Black Africans are at higher risk of having harder urinary calculi than other race groups. This has implications for urolithiasis management and highlights the importance of primary prevention in this group. We recommend additional research to confirm our findings.

Short title: Race & urinary calculi

Keywords: Characteristics; Racial disparity; South Africa; Urinary calculi; Urolithiasis.

Introduction

Urolithiasis is defined as the formation and/or presence of calculi in any part of the urinary system (1). It has been estimated that 1 in every 11 individuals residing in the United States will experience urolithiasis during their lifetime (2). Globally, the burden of urolithiasis is on the increase, and Alatab et al., postulated that the increasing global burden of urolithiasis was due to urbanization and adoption of western dietary habits by previously rural populations (3). Urolithiasis is associated with increased healthcare expenditure, and disease management in the United States alone is estimated to cost up to $2 billion annually (4, 5).

Urolithiasis can be a debilitating condition, and patients may suffer an indirect economic cost from being unable to work (6). Short term consequences of untreated urolithiasis include pain, renal colic, and haematuria. Acute disease might require hospitalization or emergency surgery (7). Long term consequences of untreated urolithiasis are more severe, and include pyelonephritis and chronic kidney disease (8, 9). Given the serious implications of urolithiasis and the growing burden of the condition, much attention has been given to understanding the underlying pathology of disease. It is well accepted that urolithiasis is multifactorial, with race being one of the proposed risk factors for the development of urinary calculi (10). Black populations have traditionally been considered as being at lower risk for urolithiasis when compared with Caucasians (11, 12). In a South African study conducted during the early 2000's, Lewandowski et al., reported that "South African blacks are relatively immune to urinary stones" (12). The authors further hypothesized that the underlying protective mechanism in South African Blacks was related to oxalate absorption (12). However, the data that this assertion was based on, may be flawed as it was based on data accrued during the Apartheid era in South Africa and may not be a true reflection of the epidemiology at the time. Non-communicable disease burden, including that of renal disease,

has increased among the Black African population in South Africa since the study of Lewandowski et al (13, 14). At the same time, non-communicable disease burden has remained static among the other racial groups comprising the South African population (14). These recent non-communicable disease trends suggest that contemporary research around differences in urolithiasis amongst the various racial groups comprising the South African population is required.

Racial differences in the risk factor profile of urinary calculi are poorly described in the South African context (11). This paucity in the knowledge limits our local understanding of urolithiasis pathology and thwarts our efforts in designing appropriate preventative interventions for high-risk groups. The objective of our study was to investigate differences in urinary calculi characteristics amongst the three main racial groups in KwaZulu-Natal, South Africa.

Materials and Methods

Research study design:

Our study was a retrospective chart review of patients attending the urology unit of a South African quaternary hospital.

Setting and study sample:

We conducted our study at the Inkosi Albert Luthuli Central Hospital (IALCH) in the Durban, South Africa. As a government-funded quaternary hospital, IALCH offers specialist healthcare services on a referral basis to the population of KwaZulu-Natal Province. The population of KwaZulu-Natal is diverse, comprised of Black Africans, Caucasians, and Asians (individuals of South Asian descent). Our study sample consisted of consecutive

patients who attended the urology unit of IALCH with urinary calculi during 1 January 2018 - 31 December 2019. Patients were identified from the admissions log maintained in the urology unit. We excluded patients who were later found to have missing data and patients of mixed ancestry.

Data collection:

We retrospectively collected data from the medical charts of patients who attended the urology unit at IALCH for management of urinary calculi during the study period (admissions and outpatients). An in-depth review of admission notes, progress notes, laboratory reports, and operation records was performed for each eligible patient. All data was entered directly onto an electronic spreadsheet. We collected data on the patient's age, sex, race, place of residence, and pre-stenting. We investigated five study outcomes across the various race groups: number of calculi, location of the calculi, size of the calculi, density of the calculi (Hounsfield Unit measurement), and the number of operative interventions performed. Calculi size was dichotomized using a threshold of 20mm (15). Hounsfield Unit measurements were dichotomized using a threshold of 600 – corresponding to a high density, calcium-based calculus (16).

Statistics:

We performed our data analysis in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Where applicable, a $p<0.050$ was considered a statistically significant result. Our statistical analysis plan included descriptive statistics for the study sample (the appropriate indicators of central tendency were reported), a crude comparative analysis between race groups (chi-squared test), and unadjusted/adjusted logistic regression analyses to investigate the probability of the various study outcomes across race groups (Odds ratios

with 95% confidence intervals). The adjusted logistic regression analysis controlled for the effects of age, sex, rural residence, and pre-stenting on the study outcomes. For the interpretation of odds ratios, an odds ratio >1.00 was considered as an indicator of increased risk for the outcome being investigated. Conversely, an odds ratio <1.00 was considered as an indicator of lower risk for the outcome being investigated.

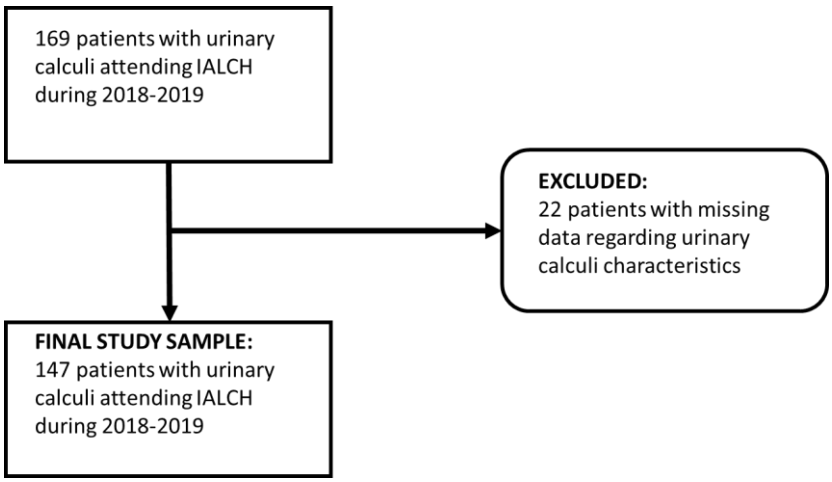
Research ethics:

Our research was reviewed and approved by the Biomedical Research Ethics Committee, University of KwaZulu-Natal (BREC/00002736/2021).

Results

After excluding 22 patients with missing data (either important characteristics or one of the study outcomes) and patients of mixed ancestry, our study sample consisted of 147 patients with urinary calculi who attended the urology unit at IALCH during 2018-2019 (Figure 1).

Figure 1. Patient flow diagram showing the derivation of our study sample (N=147)



Regarding the overall characteristics of our study sample (Table 1), the median age of study population was 49.0 years old (IQR: 36.0-58.0). There was a similar proportion of males and females (52.4% vs. 47.6%). Our descriptive analysis also revealed a multi-racial patient population (10.9% Caucasian, 55.8% Asian, and 33.3% Black African), with most of these patients residing in urban settings throughout KwaZulu-Natal. Approximately half of the study sample (48.3%) was pre-stented. Nearly 1 in every 2 patients (44.2%) had >1 urinary calculus. Most of the urinary calculi (74.8%) were located outside the kidney (ureter and bladder). Approximately 1 in every 5 patients (18.4%) had large calculi (>20mm in diameter). Around half of all patients in our study sample (49.7%) had dense urinary calculi with a Hounsfield Unit measurement >600. Lastly, approximately half of the study sample (48.3%) had >1 visit to the operating room to remove urinary calculi.

Table 1. Characteristics of our study sample (N=147)

Characteristic	**Descriptive statistic**
Age in years Median (IQR)	49.0 (36.0-58.0)
Sex, n (% of N) Male	77 (52.4)
Female	70 (47.6)
Race, n (% of N) Caucasian	16 (10.9)
Asian	82 (55.8)
Black African	49 (33.3)
Rural residence, n (% of N) No	127 (86.4)
Yes	20 (13.6)
Pre-stented, n (% of N) No	76 (51.7)
Yes	71 (48.3)
Number of calculi Median, (IQR)	1.0 (1.0-2.0)
>1 Calculi, n (% of N)	
No	82 (55.8)
Yes	65 (44.2)
At least 1 calculus outside of kidney, n (%)	
No	37 (25.2)
Yes	110 (74.8)
Largest calculi size Median (IQR)	12.0 (7.0-17.7)

Calculi size >20mm, n (% of N) No	120 (81.6)
Yes	27 (18.4)
Largest Hounsfield Unit measurement Median (IQR)	860.0 (560.0-1217.5)
Hounsfield Unit measurement >600, n (% of N) No	74 (50.3)
Yes	73 (49.7)
Number of operating room visits Median (IQR)	1.0 (1.0-2.0)
>1 operating room visit, n (% of N) No	76 (51.7)
Yes	71 (48.3)

We also conducted a crude statistical comparison of the various study outcomes across the three race groups (Table 2). The only statistically significant finding from the crude analysis was that there was a higher proportion of Black Africans who had urinary calculi with a Hounsfield Unit measurement >600 when compared with the other race groups (p=0.002).

Table 2. Crude comparison of study outcomes between race groups

Study outcome, n (% of N)	**Caucasian (N=16)**	**Asian (N=82)**	**Black African (N=49)**	**p**
>1 Calculi	10 (62.5)	33 (40.2)	22 (44.9)	0.259
Calculi outside of kidney	13 (81.2)	63 (76.8)	34 (69.4)	0.523
Calculi size >20mm	3 (18.8)	10 (12.2)	14 (28.6)	0.064
Hounsfield Unit measurement >600	***8 (50.0)***	***51 (62.2)***	***43 (87.8)***	***0.002[a]***
>1 operating room visit	7 (43.8)	36 (43.9)	28 (57.1)	0.316

[a]Statistically significant at p<0.050.

The results of our unadjusted logistic regression analysis suggested that Black Africans were seven times more likely to have a urinary calculus with a Hounsfield Unit measurement >600 when compared with Caucasians (Table 3).

Table 3. Unadjusted and adjusted odds of various study outcomes according to race group[a]

Study outcome	**Caucasian**	**Asian**	**Black African**
>1 Calculi, uOR (95%CI)	1.00 (Reference)	0.40 (0.13-1.19)	0.49 (0.15-1.53)

>1 Calculi, aOR (95%CI)	1.00 (Reference)	0.40 (0.12-1.27)	0.37 (0.09-1.37)
Calculi outside of kidney, uOR (95%CI)	1.00 (Reference)	0.82 (0.17-2.89)	0.52 (0.11-1.92)
Calculi outside of kidney, aOR (95%CI)	1.00 (Reference)	1.05 (0.21-4.02)	0.57 (0.10-2.50)
Calculi size >20mm, uOR (95%CI)	1.00 (Reference)	0.60 (0.16-2.95)	1.73 (0.47-8.39)
Calculi size >20mm, aOR (95%CI)	1.00 (Reference)	0.52 (0.12-2.72)	1.67 (0.36-9.42)
Hounsfield Unit measurement >600, uOR (95%CI)	1.00 (Reference)	1.65 (0.55-4.91)	***7.17 (2.00-27.80)[b]***
Hounsfield Unit measurement >600, aOR (95%CI)	1.00 (Reference)	2.14 (0.66-7.23)	***18.75 (3.37-157.57)[c]***
>1 operating room visit, uOR (95%CI)	1.00 (Reference)	1.01 (0.34-3.06)	1.71 (0.55-5.52)
>1 operating room visit, aOR (95%CI)	1.00 (Reference)	1.80 (0.48-7.08)	4.13 (0.89-20.70)

uOR: Unadjusted odds ratio, aOR: Adjusted odds ratio, 95%CI: 95% Confidence interval. [a]Adjusted logistic regression model controlled for age, sex, rural residence, and whether the patient was pre-stented or not; [b]p-value statistically significant (p=0.003) on unadjusted analysis when compared with reference group (Caucasian); [c]p-value statistically significant (p=0.002) on adjusted analysis when compared with reference group (Caucasian).

On the other hand, we found that the unadjusted odds of having a urinary calculus with a Hounsfield Unit measurement >600 was similar between Asians and Caucasians. When we adjusted our analysis for confounders, we found that Black Africans were almost nineteen times more likely to have a urinary calculus with a Hounsfield Unit measurement >600 when compared with Caucasians (Table 3). As with our findings from the unadjusted logistic regression analysis, there was no difference in the adjusted odds of having a urinary calculus with a Hounsfield Unit measurement >600 between Asians and Caucasians. We did not observe any other findings of interest from our unadjusted and adjusted logistic regression analyses (Table 3).

Discussion

The most important finding from our research was that Black Africans had a higher probability (7-fold higher unadjusted odds and 19-fold adjusted odds) of harder urinary calculi with Hounsfield Unit measurements >600 when compared with Caucasians. In

contrast, our finding for Asians suggests that they had urinary calculi of similar density to that of Caucasians. Therefore, we demonstrate at least one racial difference in urinary calculi characteristics between the main racial groups in KwaZulu-Natal, South Africa. A lack of difference in gender distribution was also demonstrated. Having slightly larger calculi and relatively harder calculi, there did not seem to be a significantly higher number of procedures required in this group. (Further studies may assist in ascertaining the reasons for this)

There is sparse data on urinary calculi composition in Black South Africans. It has long been assumed that hard calcium oxalate calculi are rare in the Black African racial group (11). A study of urinary calculi collected in the City of Durban during 1979-1980 reported that only 2 of the 300 calculi analysed were from Black Africans, with 1 of these confirmed as being a calcium oxalate calculus (11). The underlying mechanism conferring protection in this group is thought to be related to calcium oxalate metabolism in the gut (12). Our finding that 87.8% of urinary calculi in Black Africans had a density of >600 Hounsfield Units, and were thus likely comprised of calcium oxalate, is particularly interesting as it suggests that the hypothesized protective mechanism in this group is being overwhelmed. However, the possibility exists that lifestyle changes and risk profile have altered significantly, rendering the original hypothesis as a protective mechanism obsolete Advancements in the study of the gut microbiome have revealed that the gut of Black Africans is colonized by *Oxalobacter formigenes* and several other bacterial species capable of metabolising calcium oxalate (17). The carriage rate of oxalate degrading bacteria amongst Black South Africans is estimated at 70% when compared with 10% in Caucasians (18). Published evidence suggests a 70% reduction in the risk of being a recurrent calcium oxalate stone former in *O. formigenes* carriers when compared to non-carriers (19). The gut microbiome is sensitive to changes in diet (20). It is therefore possible that urbanization (86.4% of our study sample resided in

urban areas) and adoption of a western diet among Black Africans is slowly leading to lower carriage of *O. formigenes* and other oxalate metabolising bacteria in this racial group, placing them at risk of calcium oxalate urinary calculi. In addition, other urolithiasis risk factors may further exacerbate the reduced calcium oxalate metabolism in Black Africans with a lower carriage of *O. formigenes* or promote expansion of the urinary calculi through other known mechanisms.

While it is important that primary prevention for urolithiasis be strengthened across all racial groups in KwaZulu-Natal, it appears that additional focus must be placed on strengthening knowledge/awareness of urolithiasis and its risk factors amongst Black Africans. An intervention of this nature may promote avoidance of risk factors, such as an unhealthy diet, in this racial group and will also draw attention to the potential signs and consequences of urolithiasis such that individuals are prompted to seek healthcare services at an early stage when the urinary calculi might not be very hard (i.e., calculi with high density/ high Hounsfield Unit measurement) and easier to manage.

We did not find any other statistically significant differences between the three racial groups in terms of the other 4 outcomes investigated in our study. This might be due to the size of our study sample, which may have only allowed us to detect the strongest statistical associations between racial groups and the other study outcomes, while weaker statistical associations were missed. Another limitation of our study was that it was conducted at a quaternary hospital offering specialist care and our study sample might be very different from that of lower-level healthcare facilities were specialist care is not required. Lastly, we did not investigate long term outcomes in our study sample, as often the patients are discharged from our facility and do not return for follow-up at our outpatient clinic or their referral hospital. Such limitations must be considered when designing future research studies on this topic.

Conclusion

We found that Black Africans are at higher risk of having harder urinary calculi than the two other race groups (Caucasian and Asian) in KwaZulu-Natal. This finding has important implications for urolithiasis management in our setting and highlights the importance of strengthening knowledge/awareness of urolithiasis and its associated risk factors in this racial group. While our study provided useful contemporary information of differences in urinary calculi between the various racial groups, it was not without limitations. We therefore recommend that additional research on this topic, which will also address the limitations we have identified in our study, be done to confirm our findings.

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Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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Appendix 1: Journal guidelines

Manuscript preparation guidelines

These guidelines are based on ICMJE recommendations.

Permission and copyright: Where relevant, it is the responsibility of the authors to obtain permission from copyright holders, and to ensure that the use of images, data and illustrations in the manuscripts do not violate copyright laws. If a copyright violation in any of the published article is brought to our attention, we will notify the author for correspondence. It is the responsibility of the author(s) to settle issues with the copyright holder.

General: Manuscripts should be written in English using size 12 Roman font. The overall margin should be 2.54 cm (1 inch) with double space between lines. The manuscript should be submitted as a single file Microsoft Word document, with tables and figures inserted after the references. Also high resolution TIFF images should be uploaded separately. The page numbers should be included at the bottom right of the document. The overall guidelines are same for all article types; however, there are some minor variations for review articles, case reports and letter to editor. These are given at the end of this page. The following are the guidelines for original articles. Arrange the articles in the described order.

Title page: Title of the article, author(s), affiliation of the author(s), email of all authors and contact details of the author for correspondence.

Abstract: No more than 250 words, unstructured single-paragraph without any references. The abstract should be written in such a way that it conveys the entire message of the article.

Short title: Below the abstract include a short title (maximum 50 characters including space)

Keywords: Below the short title, include five keywords in alphabetical order, each separated by semi-colon.

Introduction: Describe why you are doing what you are doing in the light of the available literature.

Materials and Methods: Describe each method under separate headings. If relevant, include a statement about ethics approval and ethics approval number. Policy concerning ethics approval is included here. Describe the methods clearly. Mention the number of samples, equipment and chemicals used, and the number of repeats. Include the statistical methods used. Include the catalogue number of antibodies.

Results: Describe the results obtained and the level of significance. Do not repeat tabulated results in the text. Reference to tables and figures should be made parenthetically in the text, for example (Figure 1 or Table 1).

Discussion: Describe your findings but ensure that this is not a repeat of the 'Results' section. What is novel about your results? How do your results compare or contrast with the existing literature? What is your message to the scientific community?

Conclusion: Write a concluding paragraph summarising your findings and suggestions for future directions.

Acknowledgements: Acknowledge your colleagues and sources of finance that made this research possible.

Conflict of interest: Declare any conflicts of interest that are pertinent to the current manuscript. More information on conflict on interest is given here. If you do not have any conflict of interest then write "The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article"

References: The authors are not required to include doi in the reference list. The publisher will take care of it during the production stage. Use Vancouver style. References should be cited in numerical order (in parentheses) in the text and listed in the same numerical order at the end of the manuscript. If you use any software to generate references, manually verify that they are accurate and adhere to the requirements. Examples are given below (adapted from Monash University). The best way to ensure accuracy is to download from PubMed.

1. For journal articles with 1-6 authors, list all authors

Format: Author AA, Author BB, Author CC, Author DD. Title of article. Abbreviated title of journal. Date of publication YYYY Mon DD;volume number(issue number - optional):page numbers.

Example: Courthod G, Tucci M, Di Maio M, Scagliotti GV. Papillary renal cell carcinoma: A review of the current therapeutic landscape. Crit Rev Oncol Hematol. 2015 Oct;96(1):100-12. 2. For journal articles with more than 6 authors, add et al. after the sixth author

Format: Author AA, Author BB, Author CC, Author DD, Author EE, Author FF, et al . Title of article. Abbreviated title of journal. Date of publication YYYY Mon DD;volume number(issue number-optional):page numbers.

Example: Alves MR, Carneiro FC, Lavorato-Rocha AM, da Costa WH, da Cunha IW, de Cássio Zequi S, et al. Mutational status of VHL gene and its clinical importance in renal clear cell carcinoma. Virchows Arch. 2014 Sep;465(3):321- 30.

3. Book

Format: Author AA. Title of book. # edition [if not first]. Place of Publication: Publisher; Year of publication. Pagination.

Example: Carlson BM. Human embryology and developmental biology. 4th ed. St. Louis: Mosby; 2009. 541 p.

4. Chapter in a book

Format: Author AA, Author BB. Title of book. # edition. Place of Publication: Publisher; Year of publication. Chapter number, Chapter title; p. [page numbers of chapter].

Example: Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; c2005. Chapter 29, Endometriosis; p. 1103-33.

5. Edited Book

Fo*rmat:* Editor AA, Editor BB, editors. Title of book. # edition[if not first]. Place of Publication: Publisher; Year. Pagination.

Example: O'Campo P, Dunn JR, editors. Rethinking social epidemiology: towards a science of change. Dordrecht: Springer; 2012. 348 p.

6. Chapter in an edited book

Format: Author AA, Author BB. Title of chapter. In: Editor AA, Editor BB, editors. Title of book. # edition. Place of Publication: Publisher; Year of publication. p. [page numbers of chapter].

Example: Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 16578.

Tables: All tables should be created with the 'insert table' function of Microsoft Word. Tables should fit within the page margin (2.54 cm or 1 inch). The tables should be cited in numerical order in the text (Table 1, Table 2 etc). Each table should have a table number and a descriptive title above the table. Explanations for abbreviations and levels of significance should be given at the bottom of the table as letters in superscript (for example a, b, c etc), not as symbols (for example @, # etc.). Insert table(s) immediately after the references.

Figures and figure legends: All illustrations are referred to as "Figures" and must be numbered consecutively, for example (Figure 1, Figure 2 etc). Photomicrographs should be high resolution TIFF images (minimum 300 dpi). After creating the images as highresolution TIFF images, use the 'insert picture' function of the Microsoft Word to insert figures at the end of the article immediately after the tables. Provide figure legends including figure number, a short title and description immediately below each image. Also upload the figures separately during submission process. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Units: Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be in degrees Celsius. Blood pressure should be in millimeters of mercury.

Abbreviations and Symbols: Use only standard abbreviations. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Review articles: The style, title page, abstracts, tables, references and quality of images are similar to the above guidelines. The article should be organized in the following order: Title page, Abstract, Introduction, Contents under various subheadings, Conclusion, Acknowledgements (if relevant), Conflict of interest, References, Tables, Figures, and Figure legends below respective figures. A review article can be between 3000 and 5000 words, excluding the abstract and references. Do not number the headings.

Case reports: The style, title page, abstracts, tables, references and quality of images are similar to the above guidelines. Write the case report under four major headings – introduction, case report, discussion and conclusion.

Letter to editor: Comments about any of the articles that had been published in JRENHEP can be submitted as letter to editor. The word limit is 500 including references. These will undergo independent peer review and sent to the author for correspondence of the article in question. After exchange between the authors through the editorial support staff, the letter along with the response of the authors will be published.

Appendix 2: Protocol

University of KwaZulu-

Natal College of Health

Sciences School of

Clinical Medicine

Title: A retrospective chart review of the demographics of patients presenting with renal calculi to Inkosi Albert Luthuli Central Hospital urology department over a 2-year period

Degree: MMed Urology

Principal Investigator: Dhesigan

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EXECUTIVE SUMMARY

Urinary stone disease (USD), also known as urolithiasis is defined as the formation and or presence of calculi in any part of the urinary system (kidney, ureter, bladder, or urethra) The burden of this disease impacts adversely, both on patients' lives and livelihoods, as well as financially on the health sector. Patients may present with features of pain, haematuria, recurrent infection, or chronic kidney disease. The treatment of
USD usually requires specialized urological services that are both scarce and costly.

The aim of this retrospective chart review is to describe the demographics of patients presenting with renal calculi over the period 1 January 2018 - 31 December 2019 in eThekweni, and the prevalence co-existing metabolic problems in these patients.

Benefits of our study include:

- By establishing risk factors in population groups, preventive measures can be advised and implemented accordingly
- Targeted heath awareness and early management can prevent renal stone disease and reduce long-term complications.
- Determining risk factors to stone formation may aid in public health intervention, thus reducing the burden of renal stone disease and resulting in a reduction in the cost of renal stone disease management.

Background:

Urinary stone disease (USD) presents in all races, sex, and age groups. This disease process results in patient morbidity, mortality and imposes a huge burden on our cash strapped healthcare facilities.

To date there exists limited research into the demographics of USD in the eThekwini region in South Africa. Establishing a regional profile would enable us to identify risk factors for USD. These risks factor can then be modified to reduce impact of this disease.

Literature review:

Urinary stone disease (USD), also known as urolithiasis is defined as the formation and or presence of calculi in any part of the urinary system (kidney, ureter, bladder or urethra). In the United States, 1 in 11 individuals will experience a urinary stone in their lifetime (1). The prevalence of USD is estimated to be 10% to 15%, with a lifetime risk of stone formation exceeding 12% to 14% in men and 6% in women (2). There is a high probability of recurrence, with up to 50% experiencing a recurrence within 5 years. Its prevalence has doubled over the past 15 years (2) The incidence and prevalence of USD is on the increase across the world. Alatab et al (3) concluded that an increase in affluence and adaptation of the western diet habits in developing countries have seemed to contribute to these changes.

The high incidence and prevalence of USD in America and the cost of urolithiasis is estimated at almost $2 billion annually (4). It appears to be increasing with time despite a shift from inpatient to outpatient treatment and the emergence of different treatment modalities. This may be as a result of the increasing prevalence of stone disease (5). In the acute setting of urinary stone disease, many patients present to the emergency department or require hospitalization. Patients may have classic symptoms of renal colic and haematuria. However, others may be asymptomatic. Wippisinger et al (6) demonstrated the existence of asymptomatic ureteric stones with a proportion of these patients exhibiting some degree of hydronephrosis. The presence of hydronephrosis in this group implies that despite not having any symptoms of the disease, features of obstructive uropathy resulted. USD affects both adult and paediatric

population groups. Untreated USD in children may result in severe pain, urinary tract infection, haematuria and renal damage, eventually causing renal failure.

One of the studies done in the paediatric group, by WK Cheah et al (7), consisted of two cohorts of Australian children, an Aboriginal group and a non-Aboriginal group. The Aboriginal group (2.8 years average age) presented with urinary tract infections and failure to thrive. The older non- Aboriginal group (6.7 years average age) presented with flank pain. Most of these patients underwent surgical intervention.

USD causes recurrent urinary tract disease. This includes pyelonephritis, and chronic kidney disease which may require expensive renal replacement therapy. The incidence of USD in the dialysis population was found to be 5-13% (8). Another complication of USD is the development of Diabetes mellitus. Chung et al (9) identified an increased risk of Diabetes mellitus in newly diagnosed urinary stone disease patients. The cost burden of USD is a result of the cost of diagnosing the disease, the cost of managing the disease and as well as the indirect economic cost as a result of lost productivity due to incapacity leave taken as a result of symptomatic USD or as a result of recuperation from the treatment modalities of USD. Diagnosis of USD entails clinically assessment and imaging of the urinary tract. Imaging modalities include plain film abdominal Xray, ultrasound and non-contrast CT scan, the latter being the gold standard for diagnosis. However, many patients will have a plain X-ray and ultrasound as initial screening investigations before a non-contrast CT is performed resulting in the high cost of diagnosis.

Management modalities of USD comprises conservative measures and surgical options. Failed conservative management, (i.e., recurrent pain, nausea, vomiting and stone persistence) requires surgical intervention. Common surgical options employed are extracorporeal

shockwave lithotripsy, ureteroscopy (URS) and percutaneous nephrolithotomy. URS was shown to be most used by younger urologists and ESWL more used in senior urologists (10). The advantage of URS over ESWL is better stone-free rate with URS. This translates to fewer retreatments and thus is more cost- effective. Cone et al (11), demonstrated single procedure stone-free rates for SWL and URS were 47.1 and 88.7 % in patients with ureteral stones smaller than 1.5cm.

USD incidence is influenced by a multitude of factors including the age of a patient, hereditary genetic factors, race, body mass index, climate, dietary intake and water consumption. Identifying a link between these variables and the disease occurrence will decrease the associated morbidity and high economic implications of USD if this causative link can be translated into preventative strategies. Much about USD formation is still not clear. Renal cell injury, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitors or promoters play important roles for kidney stone formation (12). Addressing these factors may result in the adaptation of new management models thus preventing long-term complications of the disease. More effective drugs are likely to be developed based on better understating of the molecular changes found in USD formation.A correlation between USD and race exists. Akoudad et al (13) assessed differences in correlates across White and African men and women. They identified novel correlates of kidney stone disease (triglycerides, gallstone disease) and risk factor interactions by race (age, male sex, triglycerides, gallstone disease). A strong association of USD with an increased serum triglyceride level, older age, and gallstone disease was found in African Americans compared to whites, whereas male sex showed stronger association with USD in the white race.

Not much extensive research into USD in Africa exists, due to limited resources. Urinary tract stone disease is rare in the Negroid race, as confirmed by this study on Nigerians (14). In this study, eighty-one cases of urinary tract calculi in Nigerians seen at the University of Nigeria Teaching Hospital, Enugu, Nigeria, over a period of five years were reviewed. A relative incidence of 13 per 100,000 was established. Thirty-six stones were found in the bladder, 21 in the kidneys, 20 in the ureters, one in the prostate and 3 in the urethra. Five patients had calculi at multiple sites. There was a male to female ratio of 5:1. Forty-one per cent of the calculi occurred in the 31–40-year age group, and 14.8% of cases were found in children. Over 80% of the calculi were secondary to obstruction, infection and immobilization. Only 15% were idiopathic.

Lifestyle modification assists in USD stone prevention, with drinking sufficient water to prevent dehydration being an established preventative measure. The recurrence of kidney stones within 5 to 7 years is approximately 50%. Low urine volume is the most common abnormality and the single most important factor to correct, so as to avoid recurrences, diets low in salt (<50mmol/day) and animal proteins (<52gm/day) are helpful in decreasing the frequency of recurrent calcium oxalate stones (15).

Locally, in KwaZulu Natal, Goad et al (16) demonstrated an increase in the confirmed diagnosis of renal disease in White and Indian population groups. Further studies may show an increase in the prevalence of USD in the Black South African population. In South Africa the Black South African population comprises approximately 46.66million people (17). Prevention of USD in this population group will not only translate into massive healthcare savings in a resource strained environment but more importantly improve quality of life in these patients.

Study design:

A retrospective chart review.

Study population:

New patients presenting with renal calculi over the period 1 January 2018 -31 December 2019 in eThekwini.

Sample size:

The sample size will be approximately 200 patients

Inclusion/Exclusion criteria:

Inclusion:

All new patients presenting with renal calculi to Inkosi Albert Luthuli Central Hospital (IALCH) for the period 01/01/2018 - 31/12/2019 will be included.

Exclusion:

Existing patients presenting for repeat consultations will be excluded and patients of mixed ancestry.

Data collection and methods:

Pertinent data from outpatient records will recorded onto data sheets (1sheet/patient)

Data sheets will be stored in a lever arch file and kept in a locked cupboard that only the principal investigator has a key to.

Data will be captured into Excel for analysis with statistical software. The computer will be password protected.

Records will be de-identified.

Data analysis technique:

Descriptive statistics will be used to summarize the data. Frequencies and percent will be used for categorical data, such as race, sex, treatment. Frequency distributions of numeric data, such as size and density of stone will be examined for normality and means (SD), or medians (IQR) used as appropriate. Subgroup comparisons of the characteristics of kidney stones by demographic characteristics such as race will be done using Chi Square tests for categorical data and ANOVA or Kruskal Wallis tests for numeric data. Stata v15.1 will be used in the analysis.

Study location:

Inkosi Albert Luthuli Central Hospital

Sample size:

200 patients

Study period:

The study involves 200 patient electronic charts that will be analysed in batches of 40, thus totalling 5 data collection episodes. This will be over a period of 5 weeks. Analysis of data and report will be done as soon as data is collected.

Proposed time frames:

BREC approval: February – March 2021

Hospital gatekeeper permission: March 2021

Data collection: March – April 2021

Data analysis: May 2021

Write-up: June – July 2021

Limitations to Study

Patients may not present to their base hospitals for USD

Patient may pass renal stones spontaneously before being consulted Patients may demise prior to referral of consultation

Patients may be treated conservatively at the base institution Patients may default or miss their urology appointments

Ethical consideration:

Data sheets will be stored in a lever arch file and kept in a locked cupboard that only the principal investigator has a key to. Data will be captured into Excel and password and stored on password protected computer. Records will be de-identified. Patient consent will not be required as this a retrospective study. All patients who meet the inclusion criteria will be enrolled into the study. Submission to the ethics committee at the University of Kwa-Zulu Natal will be made. The hospital ethics committee at Inkosi Albert Luthuli Central Hospital will consulted for site approval at the study location.

Study significance

This study will demonstrate the demographics of patients presenting with renal calculi over the period 1 January 2018 - 31 December 2019 in eThekwini. The study will describe co-existing metabolic problems in these patients. Addressing these factors will improve how efficiently renal stone disease is managed in our setting.

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Appendix 3: Ethical approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

10 September 2021

Dr Dhesigan Naidoo (211560830)
School of Clinical Medicine
Medical School

Dear Dr Naidoo,

Protocol reference number: BREC/00002736/2021
Project title: A retrospective chart review of the demographics of patients presenting with renal calculi to Inkosi Albert Central Hospital urology department over a 2 year period.
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 10 September 2021. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Amended_Lockdown_Level_3_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 10 September 2021. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 12 October 2021.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee