Comparative Analysis of Kidney Stone Composition in Patients from Ghana and South Africa: Case Study of Kidney Stones from Accra and Cape Town

by

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Abstract

Aim: The primary aim of this study was to describe and compare the kidney stone composition of kidney stone patients receiving treatment at the Korle-Bu Teaching Hospital (KBTH), Accra (Ghana) and Groote Schuur Hospital (GSH), Cape Town (South Africa).

Methods: The study was a retrospective folder review of patients treated for kidney stone disease at the Korle-Bu Teaching Hospital in Accra (Ghana) and Groote Schuur Hospital in Cape Town (South Africa). Patients who were treated for kidney stone disease between 1st June 2016 and 31st May 2018 were recruited and their folder numbers were retrieved from theatre log books. A total of hundred and sixty-three (n=163) folders (n=30 KBTH; n=133 GSH) were subsequently retrieved from the records department of the two facilities. Demographic data and kidney stone analysis results were extracted and analyzed using the *R* statistical software.

Results: The age of participants at the KBTH ranged from 24 to 75 years with a median age of 45 years, while the ages of participants at the GSH ranged between 19 to 77 years with a median age of 48 years. Males were the majority stone formers for both hospitals [56.7% KBTH; 59.4% GSH]. However, there was no significant statistical difference in gender (p=0.9447) and age (p=0.2612) between the two groups. Calcium oxalate (86.7%) and uric acid (90.0%) were the commonest components of the kidney stones analyzed from the KBTH. Calcium oxalate (66.2%) and carbonate apatite (40.6%) emerged as the most common components of the stones analyzed from the GSH. Brushite (3.0%), cystine (3.8%) and struvite (19.6%) stones were only found in the stones of participants receiving treatment at the GSH. All kidney stones from the KBTH were mixed; made up of at least two chemical components. Pure kidney stones were only found among the GSH dataset constituting 48.9% of all the stones analyzed. While all KBTH stones were mixed stones, female patients from GSH formed more mixed stones than their male counterparts (M:F = 40.5%:66.67%). Infection kidney stones (struvite and carbonate apatite) were also predominantly found among female stone formers in this study.

Conclusion: The findings indicate that the participants from the two facilities are not different in terms of gender and age. However, the composition of stones was found to be different between participants from both hospitals. This suggests that that kidney stone composition may be influenced by patients' geographical location and/or cultural background. Further studies with prospective or longitudinal data and larger samples are needed to provide more insight into the composition of kidney stones of African patients.

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Abbreviations/Acronyms

ATR	Attenuated Total Reflection
BP	Blood Pressure
CA	Carbonic Anhydrase
CaOx	Calcium Oxalate
CKD	Chronic Kidney Disease
COD	Calcium Oxalate Dihydrate
COM	Calcium Oxalate Monohydrate
CT scan	Computed Tomography scan
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease
ESWL	Extracorporeal Shock Wave Lithotripsy
FN	Fibronectin
FT-IR	Fourier Transform Infrared
GSH	Groote Schuur Hospital
HA	Hyaluronic Acid
HREC	Human Research Ethics Committee
IQR	Inter-Quartile Range
KBTH	Korle-Bu Teaching Hospital
Med	Median
MDS	MDS Lancet laboratories
NS	Not Stated
OPN	Osteopontin
PCNL	Percutaneous Nephrolithotomy
PI	Principal Investigator
SS	Super Saturation
Std	Standard deviation
TGF β2	Transforming Growth Factor β2
THP	Tamm Horsffal Proteins

UA	… … … … … …	Uric acid
URS	… … … … … …	Ureterorenal Surgery
USA	… … … … … …	United States of America
UTI	… … … … … …	Urinary Tract Infection

Chapter One

1. Introduction

This chapter provides relevant background information and defines the problem statement. It also discusses the significance of the study and presents a general overview of the methods used. The chapter ends with discussions of the major limitations of the study and definition of terms.

1.1 Background of the Study

Kidney stone disease, also termed nephrolithiasis, is a debilitating, chronic condition, which has affected people (perhaps) since antiquity. It results in great morbidity. Severe colicky flank pain, infection and loss of kidney function may occur when the kidney is obstructed by a stone. It may result in loss of working hours and productivity due to repeated patient visits to the emergency unit or urologist, especially during those acute episodes requiring admission and intervention (López & Hoppe, 2010).

Kidney stones have been shown to be associated with other chronic diseases like coronary artery disease, hypertension and chronic kidney disease (Ferraro et al., 2013; Rule et al., 2009, 2010; Sigurjonsdottir et al., 2015; Todd et al., 2012; Worcester & Coe, 2010). This had led to other investigators referring to kidney stone disease as a metabolic disorder beyond the obstructive symptoms caused by these stones. Preventing the formation of kidney stones may therefore avert some of these chronic conditions.

Kidney stone analysis is essential in the assessment of stone patients, not only in determining stone composition, but also provide a guide as to metabolic anomalies that might be involved in stone formation (Pak, Poindexter, Adams-Huet, & Pearle, 2003 and Cloutier, Villa, Traxer, & Daudon, 2014). This knowledge is important in treating kidney stone disease and also instituting measures to prevent future recurrence.

Presently, there is insufficient data in the current literature on the incidence and prevalence of kidney stone disease in Africa and in other developing countries (Raheem, Khandwala, Sur, Ghani, & Denstedt, 2017). There is also limited data on kidney stone composition in Africa. From a literature search, only one study was found to have examined the composition of kidney stone in Tunisia (Akra Alaya et al., 2012). To the best of the author's knowledge, no study has been conducted to describe and compare kidney stone composition between two African countries. In recognition of this gap, the present study sought to compare the composition of kidney stone of patients receiving treatment from Ghana and South Africa. The populace in Ghana is mainly of African descent, while that of South Africa includes people of African, European, Asian ancestry and Coloured[1] people. This multi-race scenario in South Africa also presents an opportunity to understand stone composition beyond just a single race and if possible, identify the significance of stone composition and its impact on the nature of kidney stone disease in Africa.

The knowledge of stone composition is very important in further investigation and treatment of patients with kidney stone disease due to the high recurrence of this condition (Samuell & Kasidas, 1995). Kidney stone composition may also reflect the underlying medical condition contributing to the formation of stones (Pak et al., 2003). The conclusions and recommendations that would be made may help to advise patients and people at risk of forming renal stones, on necessary preventive measures to reduce the prevalence and recurrence of this condition. Therefore, the purpose of this study was to describe and compare the kidney stone composition of kidney stone patients receiving treatment at the Korle-Bu Teaching Hospital (KBTH), Accra (Ghana) and the Groote Schuur Hospital (GSH), Cape Town (South Africa).

1.2 Problem Statement

The prevalence of kidney stones has been rising globally over the past two decades due to dietary and lifestyle changes (Afshar et al., 2015; Ekeke & Okpani, 2018; Scales, Smith, Hanley, & Saigal, 2012; Scales et al., 2012). Although, studies have reported a low incidence of kidney stone disease in people of African descent compared with, for example, Caucasians, there is also paucity of information regarding kidney stones and stone composition among Africans (Lewandowski & Rodgers, 2004; Rodgers, 2006).

Evidently, the incidence of stone disease varies with race, ethnicity, occupation, geographic location, climate and diet (López & Hoppe, 2010). These factors and variations in cultural practices and diet also affect the chemical composition of kidney stones. For example, people

[1] "Coloured" is a term used in South Africa to denote a particular race or ethnic grouping that are primarily of mixed race. In South Africa (particularly Cape Town), they mostly Afrikaans speaking people. The population are most dominant in the Cape (Western Cape).

from South-East Asia consume betel leaves, nuts and calcium hydroxide paste which have been associated with hypercalciuria and hypocitraturia. Individuals from Northern India lack intestinal Oxalobacter formigenes, hence they are unable to metabolize dietary oxalate which causes absorptive hyperoxaluria (Campschroer, Zhu, Duijvesz & Grobbee, 2014; López & Hoppe, 2010). Although, calcium oxalate stones are reported as the most common stone type, the composition of renal stones varies from one country to another (Campschroer, Zhu, Duijvesz & Grobbee, 2014; Durgawale et al., 2010). For example, in a study at Maharashtra (India) 71% of the stones were composed of struvite (Durgawale et al., 2010). In Okinawa (Japan), 82% of the stones contained calcium oxalate and only 58% of analyzed stones were pure calcium oxalate (Hossain et al., 2003). In a Tunisian study, calcium oxalate monohydrate was the most common stone type and accounted for 51% of analyzed stones (Akra Alaya et al., 2012).

Anecdotal evidence shows that numerous cases of upper urinary tract stones are managed by physicians in clinics across Africa. However, at present, no published study has compared the stone composition between two different African countries. It is on this premise that this study was conducted to determine the composition of kidney stones in our sample (of patients from Korle-Bu Teaching Hospital, Ghana and Groote Schuur Hospital, South Africa) and compare the results of these two countries.

1.3 Significance of the Study

There is very limited literature on kidney stone composition in Africa. Evidently, there is no study in Ghana or South Africa on kidney stone composition. The aetiology of kidney stone formation is associated with some metabolic abnormalities, therefore, stone composition may be predictive of the underlying pathologic processes. Kidney stone disease is on the rise globally and gradually becoming a problem of public health concern, hence understanding the anomalies involved in stone formation may help institute measures to treat and prevent recurrence of upper tract stones. This study brings to bear the type(s) of stones formed in the two countries and might serve as educational and a diagnostic tool. It also sets the stage for the development of further (future) research regards kidney stone composition in African countries as well as unanswered questions that arose from this study.

1.4 Overview of Methods

This study was a retrospective folder review of patients treated for kidney stone disease at the Korle-Bu Teaching Hospital in Accra-Ghana and the Groote Schuur Hospital in Cape Town South Africa. Patients who were treated for kidney stone disease between 1st June 2016 and 31st May 2018 were recruited for the study. Theatre log books from the two hospital were reviewed to retrieve folder numbers of patients who were treated. Folders of patients were retrieved from the records department and data on demography (age, gender, occupation and country of origin) and kidney stone analysis results were obtained from the Human Research Ethics Committee (HREC) approved urology database of the two hospitals. The data was captured using data sheets (see Appendix 1) and was then entered into an Excel spreadsheet. The next stage was the cleaning of the data (to eliminate errors), coding and then exporting it into the statistical package R for analysis (R Core Team, 2017).

1.5 Limitations of the Study

This study did not consider the metabolic abnormalities nor the 24-hour urine studies, which are associated with stone formation. If it did, such consideration may have given insight as to why certain stones where formed. This was not an objective of this study but can however be the focus of future studies into comparative analysis of stone composition among different African countries. Furthermore, urinalysis and urine culture are not included in this study though they also affect stone formation and can also be used to assess treatment and follow up on patients with regards to urine pH and specific gravity.

Lastly, the study used results of stone analysis of patients who were treated in the two hospitals only. Though other institutions also treat patients with stone disease such patients have not been accounted for in this study. Hence the data used for the study might not be as representative of the entire population in Ghana and South Africa. In order to avoid losing additional power in the inferences of this study and in response to the restrictions of the small (especially, Korle-Bu Teaching Hospital) data size, investigations about interaction between multi-component kidney stones and patient demographics are left for future studies. Due to the small data size from Korle-Bu we were unable to stratify age into groups (decades) to determine the incidence of kidney stone disease among different age groups.

Notwithstanding the aforementioned limitations, this study set the platform for future collaborative studies between hospitals and laboratories in Africa to determine the incidence of urolithiasis in Ghana and South Africa (and other countries on the continent) on a much broader scale.

1.6 Definitions and Use of Terms

Many of the terminologies used in this dissertation are generic and globally understood, especially in the field of urology/medicine. Kidney stones are also referred to as renal stones: in the dissertation, they are used interchangeably without difference in definition. The following terms are also used interchangeably without difference in meaning:

- Urolithiasis/Urolith is also referred to as Urinary tract stone;
- Calculi is plural for stone;
- Upper tract urolithiasis is also referred to as Ureteric and kidney stones.

Calcium apatite, also known as Calcium phosphate, is loosely referred to as hydroxyapatite, calcium. Apatite and hydroxyapatite were used interchangeably in the text.

Chapter Two

2. Literature Review

2.1 Introduction

This chapter discusses the epidemiology of kidney stone disease, the risk factors associated with kidney stone formation and different types of kidney stones. The sub-sections also detail the composition of stones and the metabolic defects which relate to stone formation, common kidney stone types in some countries, methods used in the analysis of stones and how knowledge of stone analysis can be used in the treatment and prevention of kidney stone disease. The chapter concludes with a summary of the major findings from the literature and how they informed the development of this study.

2.2 Epidemiology of Kidney Stone Disease

Kidney stone disease was perceived as uncommon in developing countries until recently (Ekeke & Okpani, 2018). They are now a health concern in many developing nations as it is in developed countries. As reported by some researchers (Durgawale et al., 2010; Srisubat et al., 2014; Wagner & Mohebbi, 2010), data on the prevalence of kidney stone disease in Africa is largely nonexistent but prevalence as applied to the global populace is estimated to be 2–5% of the population. The prevalence of kidney stone disease in USA alone is 8.8%. The condition is more common among men with prevalence estimated to be above 10%, and 7% for women (Adamu, Alhassan & Effa, 2015; Bensalah, Pearle & Lotan, 2008; Scales et al., 2012). Scales *et al*., (2007) have reported changing trends in prevalence by gender, i.e. there is a narrowing of the prevalence gap between male and female patients with renal stone disease. In their study, increasing numbers of female patients were reported to have developed kidney stones. They attributed this to lifestyle risk factor such as obesity which is on the rise among females. The prevalence of kidney stone disease in urban population in Italy is also reported to be about 7.5% (Primiano et al., 2014).

The peak incidence of kidney stone disease is manifested between the ages of 20 to 60 years which represents the working population of any country (Bensalah et al., 2008; Phillips et al., 2015; Worster & Supapol, 2012). It is estimated that approximately up to 40% of renal stone patients would have recurrence in 5 years, 50% at 10 years and about 80% in 20 years (Phillips et al., 2015; Samuell & Kasidas, 1995; Seeger et al., 2017; Srisubat et al., 2014; Worcester & Coe, 2010; Worster & Supapol, 2012). Due to the high recurrence rate of kidney stone disease, patients are likely to have repeated visits to the emergency unit and urologist for treatment. Coupled with the high cost of treating kidney stones, the economic implications to a patient and subsequently the country, may be substantial.

2.3 Risk Factors and Type of Kidney Stones

Epidemiological studies have attributed renal stone formation to factors such as age, sex, race, dietary habits, socioeconomic status, geographic location and industrialization. Inappropriate dietary habits like increased animal protein ingestion, salty diet and low fluid intake are associated with stone formation. An increase in animal protein consumption increases urine calcium excretion and reduces urine citrate concentration as well as low urine pH, which in effect increases the risk of stone formation (López & Hoppe, 2010; Siener & Hesse, 2002). Equally, some food substances may inhibit stone formation, for examples diet rich in fruits and vegetables, vitamin C, calcium, potassium and magnesium are associated with reduced kidney stones formation and their recurrence (Siener & Hesse, 2002; E. N. Taylor, Fung, & Curhan, 2009;Taylor, Stampfer, & Curhan, 2004). Although high vitamin C intake is associated with renal stone formation, dietary vitamin C products are also rich in potassium and hence, are not associated with increased stone formation. Supplemental vitamin C however, should be avoided in urolithiasis formers (Taylor et al., 2004).

Ambient temperature has been suggested as one of the contributing factors of kidney stone formation. This is related to geographic location as renal stones are commoner in hot and arid climatic regions or countries. With global warming and the general rise in temperatures, and its attendant climate change impacts, some researchers have also blamed the high temperatures as a driving force behind the growing incidence of urolithiasis globally (Primiano et al., 2014). It has been posited that high temperatures induce body fluid loss through perspiration with resultant reduced volumes of urine production leading to supersaturation of urine with lithogenic solutes.

The five most commonly encountered stone types include: calcium oxalate, calcium phosphate, infected or struvite stones, purine or uric acid stones and cysteine stones (Çiftçioglu et al., 1999). Generally, calcium stones are by far the most common type of kidney stones (60% to

80%) and are composed of calcium oxalate, calcium phosphate or mixed calcium stones (Assimos et al., 2014; Pak et al., 2003; Basiri, Taheri, & Taheri, 2012; Escribano et al., 2009).

The risk of kidney stone formation is associated with some metabolic anomalies, such as hypercalciuria, hyperuricosuria, hyperoxaluria, cystinuria and hypocitraturia as well as low urine volumes from inadequate fluid intake. These conditions may result in an increased excretion of stone forming salts. Urinary inhibitors like citrate, pyrophosphate, magnesium, nephrocalcin, Tamm Horsfall Proteins (THP), glycosaminoglycans, α1-acid glycoprotein, α1-microglobulin, 2-HS glycoprotein, retinol binding protein, transferrin and prothrombin are potent inhibitors of stone formation. An imbalance between excretion of stone forming solutes and the inhibitors will promote stone formation. The mechanism of urine inhibitors preventing stone formation is complex and different inhibitors are involved at different stages of stone formation. For example, fibronectin (FN) inhibits aggregation of calcium oxalate (CaOx) crystals. Glycosaminoglycans, glycoproteins, nephrocalcin, uropontin and citrate on the other hand inhibit the process of CaOx crystals adherence to renal tubular cell membrane, which is an important step involved in stone formation. Other molecules like THP, heparin, FN and transforming growth factor β2 (TGF-β2) inhibit the endocytosis of CaOx by renal tubular cells during kidney stone formation (Tsujihata, 2008),(Verkoelen, 2006). The process of kidney stone formation with regards to crystal cell interaction, crystal internalization by tubular cells and elimination from renal parenchyma has been described in the next paragraph. Some of the kidney stone inhibiting molecules exhibit dual functions, for example THP in alkaline urine, it is a potent inhibitor of calcium oxalate monohydrate crystal aggregation but in acidic urine this molecule is a strong promoter of crystal aggregation. Osteopontin/uropontin also has a dual function, it works in conjunction with THP to inhibit nucleation, growth and aggregation of calcium oxalate stones, however, it promotes crystal cell adhesion which facilitate crystal retention and subsequent stone formation.

Another important factor involved in kidney stones formation are the molecules which keep crystals aggregated together. The organic substances which hold crystals together are often referred to as matrix. The matrix of kidney stones is usually made up of proteins, of which albumin forms majority. Albumin, which is involved in crystals adhesion, is the major organic substance found in all type of kidney stones. Phospholipids from cell membranes also play an important role as organic matrix in kidney stone formation especially in CaOx and calcium phosphate stones (Alelign & Petros, 2018). Other examples of these crystal binding molecules are hyaluronic acid (HA), osteopontin (OPN) and prothrombin fragment 1 (Verkoelen, 2006). In some cases, matrix forms the bulk of the kidney stones. This is often the case with infection stones which are associated with chronic urinary tract infection. The proteinaceous materials incorporated into matrix stones are THP, nephrocalcin, a γ-carboxyglutamic acid rich protein, glycosaminoglycans, albumin, mucoprotein and free carbohydrate. The driving force promoting crystal formation and subsequent kidney stones is urinary supersaturation with stone forming elements. The mechanism involved in the pathogenesis of urolithiasis in supersaturated urine commences with crystal nucleation, crystal growth, crystal aggregation and eventual stone formation (Tsujihata, 2008). Contrary to the supersaturation (SS) theory as the sine qua non for stone formation, Rodgers (Rodgers, 2014) in his study of SS in healthy subjects and stone formers, suggested that SS per se might not be the sole contributing factor to stone formation. Of note in his study, SS values varied widely in both healthy subjects and stone formers and there is also significant overlap between these groups as well. Hence SS cannot be used to segregate healthy subjects and stone formers.

Despite advances made in the study of kidney stone disease, there is still great controversy about the mechanism of crystallization and particle retention that culminates in stone formation. There are two theories which seek to explain this; the Free and Fixed particle theory. The Free particle theory was proposed based on studies that used rats as test subjects. These studies suggest that with SS of stone forming solute, crystal aggregates grow faster to obstruct the ducts of Bellini (Verkoelen, 2006). This theory has however been challenged by some investigators, considering the fact that the diameter of renal tubule is 15 to 60μm, crystals growth at a rate of 1 - 2μm/min and the transit time of urine across the kidney being 5 – 10 mins. The transit time of the crystals is too short for crystal aggregate to grow large enough to get stuck and result in stone formation (Tsujihata, 2008). The Fixed particle theory on the other hand is supported by investigators as the plausible mechanism of stone formation. This theory hypothesized that, there is initial crystallization of solute in renal tubule, then subsequent renal tubular cell damage caused by some oxidative stresses or by oxalate toxicity and ensuing crystal – cell interaction results in endocytosis of crystals into tubular cells. There is a subsequent crystal constellation transmigration to the interstitium of renal papilla which is then processed for elimination regardless of stone formation status of an individual. Stone formers have a reduced ability to eliminate these parenchymal crystals within the papillary area of the kidney. This eventually results in stone formation (Verkoelen, 2006; Tsujihata, 2008; Matlaga et al., 2007; Okada et al., 2018). It appears that in the pathogenesis of kidney stone formation, crystal – cell interaction and renal tubular cell injury are critical steps in crystal retention in early stages of stone formation. Metabolic syndrome patients (diabetes mellitus, obesity, hyperlipidaemia and high blood pressure) are predisposed to hyperoxaluria (Sakhaee et al., 2012), which in effect is associated with renal tubular cell injury due to the oxidative stresses caused by oxalate toxicity. This in part is responsible for the high incidence of calcium oxalate kidney stones formation in these group of patients.

Urinary pH is a major risk factor for kidney stone formation as it affects the solubility of various metabolites and solutes involved in stone formation. In acidic urine, uric acid and cystine are insoluble, hence low urine pH promote uric acid and cystine containing stones. High urine pH however, is associated with calcium phosphate stone formation (Wagner & Mohebbi, 2010; Sakhaee, 2007). The pathophysiologic mechanism involved in acidic urine production in uric acid stone formers is complex but believed to be linked to a defect in urinary ammonium excretion and an increased endogenous acid production attributable to renal insulin resistance. For high pH, this is associated with distal renal tubular acidosis and also the increased usage of alkaline citrate treatment for calcium oxalate (CaOx) stones (Sakhaee, 2007). Topiramate a drug used as prophylaxis for migraine headaches and the treatment of seizure disorders is a known inhibitor of carbonic anhydrate isoenzyme (CA) II and IV is also associated with alkalinization of urine, therefore users may have higher incidence of stone formation (Sakhaee, 2007).

Weight gain and obesity has been found to be associated with an increase in the incidence of kidney urolithiasis, specifically uric acid stones (Scales et al., 2012; Taylor, Stampfer & Curhan, 2013). There is an inverse relationship between BMI and urine pH, hence obese subjects turn to produce more acid urine (Taylor & Curhan, 2006). Diabetes mellitus has also been found to be associated with an increased risk for kidney stone formation. Sakhaee *et al* (Sakhaee et al., 2012) in their paper, showed clearly that patients with metabolic syndrome (DM, obesity, hypertriglyceridaemia, high BP) are predisposed to increase excretion of urine oxalate which increases their risk of CaOx stone formation. It has also been clearly demonstrated that kidney stone formers have a higher risk of developing type 2 diabetes in the foreseeable future (Taylor, Stampfer, & Curhan, 2005). Obese subjects and diabetic patients have renal tubular insulin resistance in common. This is due to defective renal ammonium production and excretion which eventually favours acidic urine production (Sakhaee, 2007; Taylor et al., 2005; Taylor et al., 2013).

Infection stones (struvite, carbonate apatite and ammonium urate) which are formed in the presence of urease producing bacteria (proteus, pseudomonas, klebsiella, corynbacterium spp) commonly occur in alkaline urine. For example carbonate apatite and struvite stones start to precipitate at urine pH greater than 6.8 in the presence of urease producing bacteria which persistently make the urine alkaline (Skolarikos et al., 2015). Another bacterium which has been implicated in kidney stone formation is Nanobacteria. Ciftcioglu *et al* (1999) in their study of Nanobacteria and kidney stone formation observed that over 97% of kidney stones analyzed contained this bacterium giving credence to the strong association of this bacterium and kidney stones formation. This bacterium may act as nidus for apatite precipitation and subsequent formation of stone. Apatite is present in almost all renal stones and serves as a precursor or nidus on which solutes precipitate to form stones in the kidneys (Çiftçioglu et al., 1999; Hong et al., 2016). Calcium phosphate or apatite crystal deposits in the interstitium along the basement membrane of the thin loops of Henle, gradually increase in size and extend to the Bellini's ducts and to the renal papillae forming Randall's plaque. With progressive increasing size of the interstitial apatite crystals, this results in disruption of the papillary urothelium thereby exposing these plaques to urine. The exposed Randall's plaque then interacts with urine proteins like osteopontin and THP and supersaturated urine which eventually results in precipitation of solutes on the plaques surface leading to kidney stone formation especially calcium oxalate (Matlaga et al., 2007; Daudon, Bazin & Letavernier, 2015; Evan et al., 2007; Miller et al., 2008). The formation of Randall's plaque is favoured by factors such as hypercalciuria, low urine volume, reduced urinary pH and the high pH in the interstitium milieu of the inner medulla results in the precipitation of apatite (Matlaga et al., 2007).

2.4 Stone Composition and Metabolic Anomalies

Stone analysis is essential in the management of renal calculus disease. The composition of a stone may suggest underlying metabolic anomalies involved in stone formation. Calcium oxalate monohydrate (COM) stones are related to hyperoxaluria and calcium oxalate dihydrate (COD) stones to hypercalciuria. In stones consisting of a mixture of COM and COD, the biochemical factor involved in the crystallization is hyperoxaluria and hypercalciuria. Carbonate apatite associated with calcium hydrogen phosphate dihydrate (brushite) is a hallmark for hypercalciuria. A mixture of carbonate apatite and COD is a marker of hypercalciuria and primary hyperparathyroidism. On the other hand, an admixture of carbonate apatite and COM kidney stone is associated with medullary sponge kidneys (Cloutier et al., 2014). This knowledge can help physicians formulate treatment strategies which will reduce recurrence of stone formation.

After stone passage or removal, every patient with recurrent or increased risk of future kidney stone formation should undergo metabolic evaluation which should include 24-hour urine sample collection and analysis. There is lack of evidence as to when these metabolic evaluations should be carried out in stone patients. The general recommendation, however, is that a patient should be stone free after stone passage or removal for at least 20 days before such studies are conducted (Skolarikos et al., 2015).

In recurrent stone formers, especially, patients on alkalinizing agents calcium oxalate stones can be converted to calcium phosphate stones in subsequent stone formation if the urine is too alkalinized as a result of treatment (Mandel et al., 2003). The composition of stones in succeeding stone events may differ in approximately 21% of patients. It is thus imperative to analyze stones after each different stone event or treatment (Cloutier et al., 2014; Mandel et al., 2003). This may alert the physician that further investigation and treatment is necessary for these stone patients.

Kidney stone disease is associated with an increased risk of adverse kidney events like chronic kidney disease (CKD) and end stage renal disease (ESRD) (Todd et al., 2012; Rule et al., 2009; Sigurjonsdottir et al., 2015). Therefore, patients with recurrent or increased risk of further kidney stone formation should be monitored closely for renal dysfunction to institute measures which would avert the progression of CKD to ESRD. The mechanism by which this occurs is multifactorial. It may be related to genetic disorders associated with stone formation like primary hyperoxaluria and cystinuria; nephrocalcinosis; renal tubular damage by crystallization within tubules and from obstruction with follow-on scarring. Knowledge of pathogenesis and stone type will help prevent recurrence of stones and future kidney failure.

2.5 Kidney Stone Composition by Country

A study conducted on stone analysis in Kenya revealed that 72% of the stones were of pure calcium oxalate, the rest were of mixed composition of which calcium oxalate/bicarbonate admixture formed 22% (Wathigo, Hayombe, & Maina, 2017). In an Algerian study, calcium oxalate which is the most common stone type formed 58%, calcium phosphate 26% and uric acid 13% of stones analyzed (Sekkoum, Cheriti, Taleb, & Belboukhari, 2011). Another study at Krishna Hospital and Research Centre (Karad of Maharashtra) in India revealed that the majority of stones occurred in the upper tracts (Kidney and Ureter); forming about 51.1% of urinary tract calculi. The stones from the study in India were heterogeneous of which 71.2% contained Magnesium ammonium phosphate, 68.8% calcium oxalate and 64% calcium carbonate. This stone composition data suggests the predominance of infection stones caused by urea-splitting organisms (Durgawale et al., 2010). In a study from Tunisia, 72% of urolithiasis were also located in the upper urinary tract. Most of the stones in this study were calcium oxalate which was found in 58.8% of cases. Calcium Oxalate Monohydrate (COM) was the most frequent component of stones analyzed. Uric acid (UA) stones were also reported to be of high occurrence in this study and constituted about 21% of the stone cases analyzed (Alaya et al., 2012). A similar study on the composition of urinary tract calculi among kidney stone disease patients in Okinawa (Japan) revealed that 81.6% of the stones were calcium oxalate and contained as high as 15.8% uric acid stones. Pure calcium oxalate stones in this study constituted 40% (monohydrate 21%, dihydrate 6.6% and combined monohydrate and dihydrate stones 12.4%) and majority of mixed stones were composed of calcium oxalate and calcium phosphate stones (35.3%) (Hossain et al., 2003). Out of the 232 stones analyzed in a Pakistani study (on composition of renal calculi), 87.5% contained calcium oxalate. Of the pure stones, calcium oxalate constituted about 51.7% of all stones analyzed and only one stone was of pure uric acid. Notably, all stones in this particular study contained oxalate and 99.5% calcium as constituents (Bangash, Shigri, Jamal, & Anwar, 2011).

The analysis of kidney stones among 300 subjects, with ages less than 20 years in Tunisia, revealed calcium oxalate as the major constituent (53%) of the stones studied. In the same study Ammonium urate was the second most common chemical constituents of the stones (Alaya et al., 2011). Another study that presented an overview of kidney stone disease among 550 respondents in Lebanon concluded that calcium oxalate and uric acid stones formed 86% of stones studied. Cystine stones, however, were the least common component of the analyzed stones in the study population (Cherfan, Safwan & Sakr, 2016). In an Iranian study, which evaluated the relationship between hardness of tap water and composition of upper tract urolithiasis, all stones in the study, but one, were mixed. Calcium oxalate was, however, the major chemical component of the stones which were investigated (Moslemi, Saghafi & Joorabchin, 2011). These and other studies suggest significant differences in stone composition in different countries.

2.6 Methods of Kidney Stone Analysis

Kidney stone analysis is very important not only in determining the composition of uroliths, it also helps in the understanding of the physicochemical process involved in the pathogenesis of stone formation, treatments for stone disease and prophylactic measures to be instituted to prevent recurrence. There are several methods of kidney stone analysis, one of which is wet chemical analysis which was once widely used (Hodgkinson & Infirmary, 1971). Analysis of stones by this method may either be qualitative or semiquantitative. This approach of stone analysis is arduous and only able to identify cysteine and ions like calcium, ammonium, magnesium, carbonate, phosphate, urate and oxalate. It however, fails to detect xanthine, 2,8-dihydroxyadenine or drugs related stones (Basiri et al., 2012; Singh & Rai, 2014; Primiano et al., 2014). This method of stone analysis was once considered the gold standard of stone analysis but has now been found to be associated with substantial errors in the determination of stone composition in the range of 6.5% to 94% (Basiri et al., 2012; Primiano et al., 2014). The wet chemical analysis of stone, although inexpensive and easy to conduct, it is now considered obsolete and only mentioned in literature for archival purposes. The other techniques of renal stone analysis which involved the use of dry specimen are, thermogravimetry, optic polarizing microscopy, scanning electron microscopy, powder X- ray diffraction and infrared spectroscopy (Fourier transform infrared spectroscopy FT-IR, the attenuated total reflection technique ATR) (Basiri et al., 2012; Singh & Rai, 2014; Primiano et al., 2014). Fourier transform infrared spectroscopy was first used in stone analysis by Beischer in 1955. It operates on the principle that when stones are exposed to infrared radiation, some energy bands are absorbed which are unique to the stone and also based on its composition. This technique of renal stone analysis is cost effective, quicker in assessment of stones, able to quantitatively assess small specimen and distinguish them to various components, and also comes handy in the detection of non-crystalline or organic substances in stones with precision (Basiri et al., 2012; Singh & Rai, 2014; Primiano et al., 2014). Other spectroscopic techniques used to analyze stones are energy dispersive X-ray analysis, Laser-induced breakdown spectroscopy, Laser ablation inductively coupled plasma-mass spectrometry and X-ray absorption spectroscopy. Whereas FT-IR spectroscopy is employed in clinical laboratories, the other spectroscopic methods are used in research laboratories in assessing urolithiasis composition.

2.7 Kidney Stones and Preventive Management

The bedrock of kidney stone disease management after expulsion or surgical removal is the prevention of its recurrence. The role of stone analysis in the management of stone disease can thus not be over emphasized since the metabolic abnormalities associated with urolithiasis can be predicted from stone composition. The general principles involved in treating and preventing urolithiasis are:

- Increased fluid intake (2.5-3L) so as to produce large urine volumes with low specific gravity (Worcester & Coe, 2010; Bao & Wei, 2012);
- Balance diet consisting of high fibre, low salts (4-5 g/day), low meat products (restrict protein intake to 0.8-1.0 g/day) and normal calcium;
- Maintenance of ideal body weight; and
- Good daily physical activities and balancing of excessive fluid loss are essential (Skolarikos et al., 2015; Siener & Hesse, 2002; Assimos et al., 2014).

Calcium oxalate stones associated with hypocitraturia require the use of potassium or sodium citrate treatment (Worcester & Coe, 2010; Song et al., 2016; Phillips et al., 2015). The amount of citrate used, should be titrated according to daily urine pH so as to prevent over alkalinization of urine which may predispose one to the formation of calcium phosphate stones - stones that require high pH. The targeted daily urinary pH of 6.5 to 7.0 is required, this can be monitored by the patient at home with urine dipstick test. On the other hand, Calcium oxalate stones that are associated with hypercalciuria and hyperoxaluria require thiazide and pyridoxine respectively to prevent recurrence (Skolarikos et al., 2015). Pyridoxine is often administered in patients with primary hyperoxaluria in whom daily urinary oxalate excretion exceeds 1 mmol/day. On the other hand, if the hyperoxaluria is due to bowel effect (example increased dietary oxalate or short bowel syndrome) patients are required to take calcium with diet to reduce enteric absorption of oxalate. Calcium phosphate stones are often associated with hypercalciuria and also alkaline urine as may occur in primary renal tubular acidosis. Alkalinizing agents like potassium citrate can also be prescribed to these patients but with great caution since it may predispose the patient to forming more phosphate stones. Thiazide diuretics are, however, recommended in managing these patients if hypercalciuria persist despite the use of citrate to correct systemic acidosis (Skolarikos et al., 2015; Worcester & Coe, 2010; Xu, Zisman, Coe, & Worcester, 2013). Stones identified to be composed of uric acid are often formed in acidic urine medium and thus requires alkalinization of urine with citrate which increases the solubility of uric acid and consequently prevents UA stone formation and its recurrence. If the UA stones are associated with hyperuricosuria or hyperuricemia, allopurinol may be used for prevention of stone formation (Xu et al., 2013; Gul & Monga, 2014). Stones composed of cystine are usually associated with cystinuria which is insoluble in urine with low pH. This condition is an autosomal recessive hereditary metabolic disorder. The use of citrate to raise urine pH and thiol drugs like, α-mercaptopropionylglycine (tiopronin) which prevent the formation of cystine from cysteine amino acids, D-penicillamine on the other hand binds to cystine to form a mixed soluble compound (Xu et al., 2013; Gul & Monga, 2014; Goldfarb & Grasso, 2017). Keeping cystine soluble in urine is the hallmark to preventing kidney stone formation.

The infection stone (struvite or carbonate apatite or ammonium urate) is formed in urine with high pH in association with urinary tract infection. After complete surgical removal of such stones, long-term antibiotic prophyllaxis is the main preventive measure in these patients. However, the use of urine acidification agents like ammonium chloride or methionine and acetohydroxamic acid, which is a urease enzyme inhibitor, may also be used (Skolarikos et al., 2015; Gul & Monga, 2014). These urine acidification agents especially acetohydroxamic acid is rarely used to prevent struvite stone formation, because of the associated risk of systemic acidosis, thromboembolic phenomenon, anaemia, abdominal pain and headaches (Zisman, 2017).

Table 2.1: Summary of Previous Research

Author	***n***	**Target group**	**Gender ratio M:F**	**Common type of stone (%)**	**Major component of stone (%)**	**Mixed stones (%)**	**Type of study**	**Technique of stone analysis**	**Metabolic abnormalities reported**	**Location of stone**	**Country of study**	**Method of stone retrieval (%)**
Wathio *et al* 2017	67	Mixed	NS	CaOX (71.6)	CaOX (100)	Yes (28.4)	Retrospective	Wet chemistry	NS	Upper and lower tract	Kenya	NS
Sekkoum *et al* 2011	62	NS	NS	CaOX (NS)	CaOX (58.06)	Yes (NS)	Retrospective	FTIR	Yes	NS	Algeria	Surgery (62.9) Spontaneous (37.1)
Durgawale *et al* 2010	125	Mixed	NS	Struvite (71.2)	CaOX (68.8)	Yes (100)	NS	Wet chemistry	NS	Upper and lower tract	India	Surgery
Alaya *et al* 2012	1301	Mixed	1.5:1	COM (50.7)	CaOX (58.6)	NS	Retrospective	FTIR	Yes	Upper tract (81.8) Lower tract (18.2)	Tunisia	Surgery (92.2) ESWL (6.2) Spontaneous (1.3) Endoscopy (0.3)
Hossain *et al* 2003	1816	Mixed	2.7:1	CaOX (40.0)	CaOX (81.6)	Yes (41.6)	Retrospective	FTIR	NS	NS	Japan	Surgery (NS) Lithotripsy (NS) Spontaneous (NS)
Bangash *et al* 2011	232	Mixed	2.7:1	CaOX (38.4)	CaOX (87.5)	Yes (47.9)	NS	Wet chemistry	NS	NS	Pakistan	Surgery
Alaya *et al* 2011	300	Children	1.54:1	COM (46.3)	CaOX (53)	NS	Retrospective	FTIR	Yes	Upper tract (69) Lower tract (31)	Tunisia	Surgery (94.7) Endoscopy (2.0) Spontaneous (3.0)
Cherfan *et al* 2016	550	Adults	NS	CaOX (62.7)	NS	NS	NS	NS	NS	NS	Lebanon	NS
Moslemi *et al* 2011	255	Adults	4.93:1	CaOX (NS)	CaOX (73)	Yes (99.6)	Prospective	Wet chemistry	NS	Upper tract	Iran	Surgery ESWL Spontaneous

NS – Not stated, ESWL – Extracorporeal shock wave lithotripsy, FTIR – Fourier transform infrared spectroscopy, COM – Calcium oxalate monohydrate, CaOX – Calcium oxalate.

Table 2.1 summarizes key findings in literature on the analysis of urinary tract stone composition in different countries. Most of the studies cited used both children and adult subjects in the study. Stone composition in children is different from those in adults. Children tend to produce more ammonium urate (due to chronic diarrhoea associated dehydration and phosphorus deficiency) and genetic associated stones. Ammonium urate stones in most cases are endemic bladder stones. In as much as Alaya et al., (2012) have reported a rising incidence of calcium oxalate stones in children, they also found significant ammonium urate stones in children. The patho-aetiological processes involved in lower urinary tract stone formation is different from that of upper tract. However, all the studies in Table 2.1 combined both upper and lower urinary tract stones in their studies except Moslemi et al., (2011) who restricted their study to the upper tract.

The wet chemical method of stone analysis as stated earlier (methods of kidney stones analysis) (page 14) is limited because it only detects cysteine and certain ions in stones and is also beset with significant errors in determining stone composition. This was the method used in the analysis of stones by some of the investigators who reported their work on stone composition. These are likely to affect the results of the stone composition. Conspicuously missing in the above studies (and all literature searches), is the lack of comparison of stone analysis to other countries. This gap happens to be the key aim of this study and thus present new knowledge on the same.

Chapter Three

3. Aim and Objectives of the Study

3.1 Introduction

This chapter discusses the aim and objectives of the study as well as the methodology. The chapter concludes with data management and analysis.

3.2 Hypothesis

There would be no differences in kidney stone composition among patients in Accra (Ghana) and Cape Town (South Africa).

3.3 Aim

The primary aim of the study was to describe and compare the kidney stone composition of kidney stone patients who received treatment at the Korle-Bu Teaching Hospital, Accra (Ghana) and the Groote Schuur Hospital, Cape Town (South Africa).

3.4 Objectives

The objectives of the study are:

1. To describe the demography and kidney stone composition among patients receiving treatment at the Korle-Bu Teaching Hospital, Accra, Ghana;
2. To describe the demography and kidney stone composition among patients receiving treatment at the Groote Schuur Hospital, Cape Town, South Africa;
3. To compare the demographic characteristics and kidney stone composition between kidney stone patients treated at Korle-Bu Teaching Hospital and Groote Schuur Hospital.

3.5 Methods - Study Design

This was a retrospective study involving patient folder review from 1st June 2016 to 31st May 2018 at the Korle-Bu Teaching Hospital (Accra-Ghana) and Groote Schuur Hospital (Cape Town, South Africa). The study is purely a descriptive study of kidney stone composition of patients who were treated for kidney stone disease in the two hospitals over the period of 1st

June 2016 to 31st May 2018. The study also aimed to describe the demographic characteristics and kidney stone composition of patients treated in the two hospitals and compare the results.

3.6 Study Area

The study was conducted with data from the Korle-Bu Teaching Hospital (KBTH), Accra and Groote Schuur Hospital (GSH) Cape Town. KBTH is one of the largest teaching hospitals in Ghana and on average it has over 1,500 daily outpatients visit. It also has a bed capacity of about 2000 with an admission rate of about 250 per day. KBTH receives referrals from different parts of the country as well as from neighbouring countries. Groote Schuur hospital in Cape Town is the largest government funded tertiary academic hospital affiliated to the University of Cape Town in Western Cape, South Africa. It has a total bed capacity of 893. GSH receives patients from other hospitals in Western Cape and neighboring countries within the sub-region. Globally, GSH is famous for the first successful human heart transplant surgery in the world which was performed by Dr. Christian Barnard in 1967.

The urological units of these two hospitals offer specialist consultancy and management of referred urological cases including kidney stones for different people irrespective of nationality. Both units offer stone service programs to patients with urolithiasis.

3.7 Study Participants

Patients with kidney stone disease who were treated at the Urology units of Korle-Bu Teaching hospital and Groote Schuur Hospital over the study period were included in this study. The study recruited consecutive patients who were treated for stone disease in the two hospitals. All patients from the 2 hospitals who had treatment for upper tract urolithiasis and had their stones analyzed over the study period were included in the study population.

Inclusion criteria - All adult patients (18 years and above) who have been treated for upper tract urolithiasis (kidney and ureteric stone disease) in the two Hospitals and had their stones analyzed will be included.

Exclusion criteria **-** All patients below the age of 18 years; patients who passed stones spontaneously; patients without stone analysis results and patients whose folders cannot be traced.

3.8 Sampling

This was a study comparing the kidney stone types formed in patients who attended Korle-Bu Teaching hospital (KBTH) in Accra, Ghana and Groote Schuur Hospital (GSH) in Cape Town, South Africa. There was not a sufficient study population from which a statistics formula-based sample size calculation could be drawn. Thus, we did not calculate a sample size but used the available folder/data of consecutive patients who were treated for kidney stone disease and had their stones analyzed. A total of thirty (n=30) and one hundred and thirty-three (n=133) patient folders were obtained from Korle-Bu Teaching Hospital and Groote Schuur Hospital respectively. The high number of analyzed stones data from Groote Schuur Hospital can be attributed to a dedicated stone clinic which has a policy of stone analysis. The patients from Groote Schuur hospital do not pay upfront for services rendered to them, and some patients are also billed depending on income levels. The kidney stones are analyzed, and patients are billed later for services rendered. This is not the same for KBTH patients as they have to pay upfront for their stones to be analyzed. To ascertain that data from KBTH was random, the data from KBTH was verified across three demographic variables (age, gender and employment). There was no strong evidence of bias in data collected from Korle-Bu Teaching Hospital. This is discussed further in Chapter 4 under Data Verification.

3.9 Recruitment and Consent Process

The folders of patients who had surgeries for kidney stones between June 2016 and May 2018 were retrieved from the records department of both hospitals. The folders were reviewed for patients with stone analysis results and against the inclusion and exclusion criteria stated above. Informed consent was obtained for all patients prior to undergoing surgical treatment for upper tract urolithiasis. No additional consent was obtained from patients for the use of their data for the purpose of this study as the study was a retrospective and de-identified data was used. Also, informed consent for the data was not obtained from individual patients as per ethics approval for the study, as there was no further direct contact with patients – because this was a retrospective analysis of routinely collected data. Consent was however obtained from both hospitals for this study to be conducted and this was done through an ethical application (see Appendix 2 and 3).

3.10 Research Procedures

After ethical approval from KBTH and GSH was granted, data of patients treated for kidney stone disease were collected. All patients who had radiological images (X-ray and CT scan) confirmation of upper tract urolithiasis and were surgically treated, either by minimally invasive (URS, PCNL, Laparoscopy) or open surgery were recruited for this study. Theatre logbooks between 1st June 2016 and 31st May 2018 were reviewed for folder numbers of patients who had stone surgeries. These were used to source names from HREC approved urology database of the two hospitals and variable data obtained was entered into a password-protected database accessible only to the researcher.

Data on date of surgery and stone analysis, demography (country of origin, age, gender and occupation) and kidney stone composition after analysis were collected using a data sheet (see Appendix 1). The data were then entered into a Microsoft Excel spread sheet.

3.11 Kidney Stone Analysis

Stones collected from patients during surgical procedures were labelled and sent to the laboratory for analysis. Two laboratories (i.e. MDS Lancet and Pathcare laboratories) were involved in the analysis of stones for this study. Both laboratories are South African based with branches in other African countries. MDS lancet was involved in the analysis of stones from KBTH and Pathcare from GSH. MDS lancet used Thermo Scientific, **Nicolet iS10 FT-IR** (Fourier transform infrared) spectrometer and Pathcare used Agilent Technologies, **Cary 630 FT-IR** spectrometer for stone analysis. Stone specimen received by these laboratories were washed with distilled water to get rid of foreign materials or blood, air dried under room temperature and then weighed. The stones were then crushed into powder for analysis. The powdered stone sample was mixed with potassium bromide (an infrared inert substance) to form a potassium bromide pellet and then used for infrared analysis. This method of sample preparation for analysis was used by MDS lancet. Pathcare on the other hand used a technique referred to as attenuated total reflection which does not require the admixture preparation (with potassium bromide) of powered sample before analysis. The basic principle by which the FT-IR spectrometer operates had been described earlier in chapter 2 under methods of kidney stone analysis (pg.14). The following information was recorded:

- Date of kidney stone surgery
- Date of stone analysis

- Demographic data
  - Country of origin
  - Age
  - Gender
  - Employment status

- Type of kidney stone
  - Calcium oxalate monohydrate
  - Calcium oxalate dihydrate
  - Calcium phosphate
  - Struvite
  - Uric acid
  - Cysteine
  - Ammonium urate
  - Brushite
  - Other

3.12 Data Management and Analysis

3.12.1 Data handling and data entry

Data was coded and captured into Excel spread sheets and then exported into the statistical package R where it was cleaned and analyzed (R Core Team, 2017).

3.12.2 Data Analysis

Descriptive statistics such as mean, standard deviation, frequencies and percentages were used to summarize the data (eg. Age, gender, country of origin and employment status). A student t-test was used to compare differences on age variables between the South African and Ghanaian samples. Wilcoxon non-parametric test was used to determine the difference in age variable between patients who had their stone analyzed and those without among the Korle-Bu dataset. A p-value of less than 0.05 is considered statistically significant. In cases where the variable count is more than 5%, Chi-Square goodness-of-fit tests of proportions was used to assess for significance (gender variable between Korle-Bu and Groote Schuur Hospitals). The demographic variables, renal stone type, renal stone chemical composition and kidney stone analysis as function of demographic indicator was analysed and compared between the Korle-Bu Teaching Hospital and Groote Schuur Hospital.

3.13 Ensuring Ethics

Ethical approval had been sought and approved from the Surgical Divisional research committee of Groote Schuur and the Human Research Ethics Committee of both institutions. The study has been approved by these agencies (see Appendix 2 and 3 respectively for approval letters). In accordance with the ethics rules for which the ethics application was approved, no names or identifiable details of any patient were used in the study.

Chapter Four

4. Results

4.1 Introduction

This chapter reports the outcome of the statistical analyses of the data. Various comparative analyses were implemented from which conclusions were drawn. The chapter includes a section on data verification, results of the comparative and demographic analysis, kidney stone chemical composition analysis and concludes with kidney stone analysis as a function of demographic indicators.

4.2 Data Verification

The analysis of stones at Korle-Bu Hospital had to be privately carried out by the patients (patients pay upfront for services), unlike at Groote Schuur Hospital where similar stone analysis work is done fee free for some categories of patients. Those who pay for services are billed later according to income levels. Therefore, all kidney stone patients treated at Groote Schuur Hospital have their stones analysed by the hospital without the patients making any initial payment. Some patients at the Korle-Bu Hospital thus forgo the option of having their stones analysed, for example, because it is not a critical health risk to them. The reliability of inferences from subsequent analyses based on the Korle-Bu cohort data will be undermined, if patients that forwent kidney stone analysis did so due to certain pertinent demographic characteristics. This section is consequently dedicated to discussing analyses that were implemented to investigate whether there is any demographic characteristic that differentiates the Korle-Bu patients that had their kidney stones analysed and those whose stones were not analysed.

The Korle-Bu data contains records of forty-one kidney stone patients. Eleven (that is, less than 27%) of those patients have no record of kidney stone analysis. Table 4.1 contains a summary of the following three demographic variables across all the Korle-Bu kidney stone patients: age, gender and employment status.

Table 4.1: Data from Korle-Bu hospital (Accra, Ghana) summarised in terms of demographic variables.

Variable	Composition	
	Available	Unavailable
Gender n(%)		
Male	17 (0.57)	7 (0.64)
Female	13 (0.43)	4 (0.36)
Employment n(%)		
Declared	12 (0.40)	3 (0.27)
Undeclared	18 (0.60)	8 (0.73)
Age (years)		
median (IQR)	45 (19.75)	38 (17.00)
p-value	0.4095	

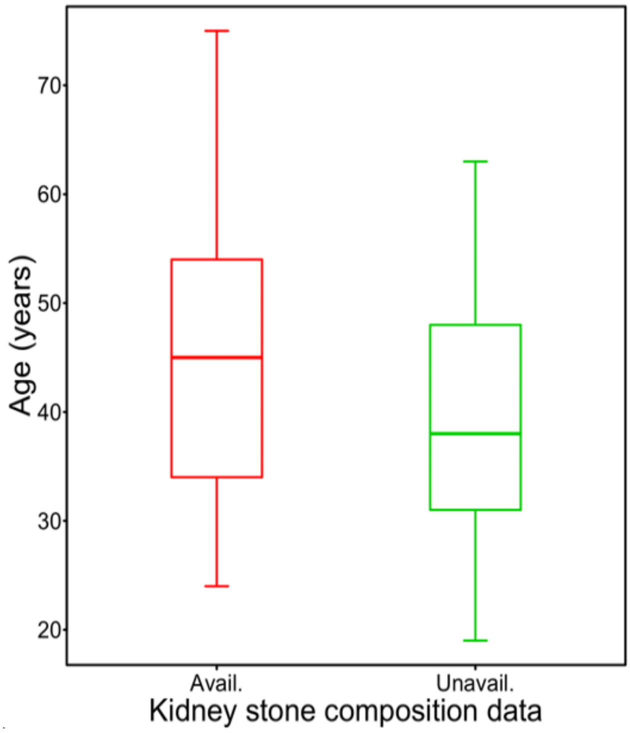

Figure 4.1: Distributions of Age among Korle-Bu kidney stone patients as a function of whether or not their kidney stone analysis data are available.

Table 4.1 contains the counts and proportions of Korle-Bu kidney stone patients with respect to the discrete variables Gender and Employment. It also contains the five-number (as well as the median and interquartile ranges) summary of the continuous Age variable. The p-value in Table 4.1 is obtained from Wilcoxon non-parametric test and it verifies the null hypothesis that the population median age across the two stone composition samples are equal. From the boxplot in Figure 4.1, the patients that failed to go for kidney stone analysis examination appear slightly younger (median age 38 years) than those that had their stones analysed (median age 45 years) however the difference was not statistically significant (p = 0.4095).

From Table 4.1, males were more likely to send their stones for analysis compared to females. However, the decision to send stones for examination seem to not be associated with gender difference. We analysed the relationship between stone analysis and employment. The records for employment were such that some patients declared their jobs, while some did not. Thus, job declaration was used as a proxy for being employed. Nonetheless, to avoid an error in assumption the terms "declared" and "undeclared" are used. It is not justifiable to assume that those who did not declare their employment status are thus unemployed. Figure 4.2 shows that majority of the kidney stone patients treated in Korle-Bu did not declare their employment status. This pattern is retained within patients that sent their kidney stones for examination and those that did not. Although, sending stone sample for examination may have economic implications to the patients, it is seeming to be a matter of choice and preference among Korle-Bu patients.

The inferences from Table 4.1 and Figure 4.1 suggest that there is no sufficient evidence in the observed Korle-Bu data to warrant fear of demographic bias between patients that did not send their stones for examination and those that did.

4.3 Comparative Analysis

Records of kidney stone composition among patients of both Korle-Bu and Groote Schuur hospitals are distributed across ten components. Table 4.2 contains an example of kidney stone analysis record for a patient in the data set. The data is recorded in terms of the percentage of the kidney stone constituted by each chemical component. This section contains details of the within- and between-sample analyses of the data sets. Employment records were unavailable for the Groote Schuur cohort. Thus, the analyses were only implemented with respect to age and gender demographic variables.

Table 4.2: Example of percentage kidney stone composition record for a patient

Ammonium Urate	**Brushite**	**Calcium Apatite**	**Calcium Oxalate**	**Carbonate Apatite**	**Cystine**	**Sodium Urate Monohydrate**	**Struvite**	**Uric Acid**	**Unknown Matrix**
0.00	0.00	24.00	40.00	0.00	0.00	0.00	26.00	10.00	0.00

4.4 Demographic Analyses

Table 4.3 is partitioned into two parts. The left part contains patient counts as a function of Gender and Hospital. The p-value in the table is obtained from Chi-Squared goodness-of-fit test and it verifies the null hypothesis that the distribution of gender is similar for both hospitals.

The right part of Table 4.3 contains a quantitative summary of age as a continuous variable for patients from Korle-Bu and Groote Schuur hospitals. The median age of Korle-Bu patients is 45 years (range 24 to 75) and for Groote Schuur is 48 years (range 19 to 77). The small difference between mean and median age (less than one year for both samples) is an indication that age data is not skewed for either cohorts. Although the range, mean and standard deviation of the Groote Schuur cohort was higher, the distributions of ages in both cohorts are similar. Student t-test p-value ($p = 0.2612$) in the table imply that there is hardly any evidence of dissimilarity between the average age of the population of kidney patients attended to at both hospitals of interest. Both the non-skewness and spread deductions from the age data are affirmed by the corresponding boxplot in Figure 4.2.

Table 4.3: Demographic characteristics of kidney stone patients treated at Korle-Bu Teaching Hospital (Accra, Ghana) and Groote Schuur Hospital (Cape Town, South Africa).

	Gender		**Age**							
					Quantiles					
	Female	**Male**	**Count**	**Min.**	**25%**	**50%**	**75%**	**Max.**	**Mean**	**Std. dev.**
Korle-Bu Counts	13	17	30	24.00	34.00	45.00	53.75	75.00	45.13	14.35
Proportion	0.4333	0.5667								
Groote Schuur Counts	54	79	133	19.00	38.00	48.00	59.00	77.00	48.44	14.54
Proportion	0.4060	0.5940								
Chi-Squared p-value: 0.9447			Student t-test p-value: 0.2612							

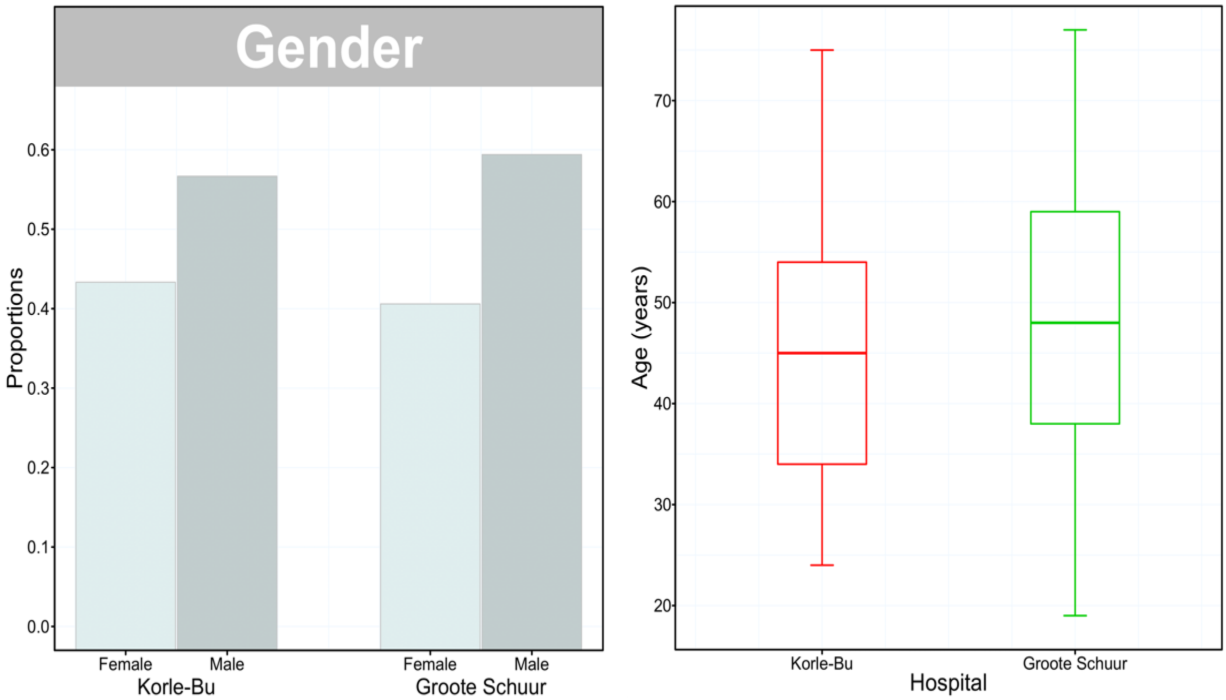

Figure 4.2: Comparisons of demographic indicators between kidney stone patients attended to at Korle-Bu Teaching Hospital (Accra, Ghana) and those treated at Groote Schuur Hospital (Cape Town, South Africa).

4.5 Kidney Stone Chemical Composition Analyses

Table 4.4 contains counts and fractions of the (30 for Korle-Bu and 133 for Groote Schuur) kidney stone patients whose stones contain each of the corresponding ten chemical components (including an unknown category) recorded in the data. Most of the kidney stones from the dataset were composed of multiple chemical components. The bold red figures represent the chemical components that were observed in the stones of more than five percent of the patients in at least one of the hospitals. The "less-than-five-percent" or "minor" (non-bold) categories are subsequently combined into a single group labelled as *Other*. The compressed table of kidney stone chemical component is presented as Table 4.5. The fractions in the compressed table are illustrated with a graph in Figure 4.3.

Table 4.4: Chemical components present in kidney stones (number and proportion) in patients treated at Korle-Bu Teaching Hospital (Accra, Ghana) and Groote Schuur Hospital (Cape Town, South Africa).

	Kidney Stone Chemical Component									
	Ammonium urate	**Brushite**	**Calcium apatite**	**Calcium oxalate**	**Carbonate Apatite**	**Cystine**	**Sodium urate monohydrate**	**Struvite**	**Uric acid**	**Unknown matrix**
Korle-Bu										
Count	1	0	**3**	**26**	**5**	0	1	**0**	**27**	1
Proportion	0.0333	0.0000	**0.1000**	**0.8667**	**0.1667**	0.0000	0.0333	**0.0000**	**0.9000**	0.0333
Groote Schuur										
Count	5	4	**0**	**88**	**54**	5	0	**26**	**27**	0
Proportion	0.0376	0.0301	**0.0000**	**0.6617**	**0.4060**	0.0376	0.0000	**0.1955**	**0.2030**	0.0000

* The bold values correspond to the compounds that were observed in more than five percent of the patients in at least one of the hospitals.

Table 4.5 Compressed kidney stone chemical composition summary of patients treated at Korle-Bu and Groote Schuur Hospital

	Kidney Stone Chemical Compound Constituent					
	Calcium apatite	**Calcium Oxalate**	**Carbonate Apatite**	**Struvite**	**Uric acid**	**Other***
Korle-Bu						
Count	3	26	5	0	27	3
Proportion	0.1000	0.8667	0.1667	0.0000	0.9000	0.1000
Groote Schuur						
Count	0	88	54	26	27	14
Proportion	0.0000	0.6617	0.4060	0.1955	0.2030	0.1053

* Other: Ammonium urate, Brushite, Cystine, Sodium urate monohydrate and Unknown matrix
NB: This table is similar to Table 4.4 except for the new class named "Other".

If chi-squared goodness-of-fit test were implemented to verify the null hypothesis that there is no interaction between the chemical composition of kidney stones and the geographic location of the patients, the result is likely to be unreliable because some of the counts in Table 4.5 are less than five. Regardless, there are numerous interesting deductions evident from the table. Overall, from Table 4.5, there is good evidence that the chemical components of kidney stones depend on the geographic location of the patient. More specifically,

a. Calcium apatite is only prevalent among patients of Korle-Bu Teaching hospital and was not observed in any of Groote Schuur hospital patients. Contrarily, Struvite is only recorded among Groote Schuur cohort while none of Korle-Bu stones contained struvite;

b. There is quite strong discrepancy between the hospitals with respect to the sample of patients that had Uric acid in their stones. Most of the stones from Korle-Bu patients (90%) contained uric acid, while only a few (about 20%) of the stones from Groote Schuur contained the chemical compound;
c. Notably more stones from Korle-Bu patients (86.67%) contained Calcium oxalate compared with 66.42% from Groote Schuur. Carbonate apatite was more common among Groote Schuur kidney stones 40.30%, while only 16.67% of stones from Korle-Bu contained Carbonate apatite; and
d. There was no apparent difference between stones from both hospitals with respect to the Other kidney stone composition category (10% and 10.45% for Korle-Bu and Groote Schuur respectively).

The analysis also investigated the number of chemical components in the stones of patients from these hospitals. Figure 4.3 is an illustration of the number of chemical components that made up the kidney stones of the patients from each hospital. It is evident that there is an interaction between the "complexity" of kidney stone and the geographic location of the patient. For example, while more than 49% of the Groote Schuur cohort had kidney stones made up of only one chemical component (pure stone), none of their Korle-Bu counterparts had pure stones. The proportion of patients who formed stones made up of 3 chemical components is however, the same for the two hospitals. One patient from Korle-Bu formed a stone which was made up of four chemical components.

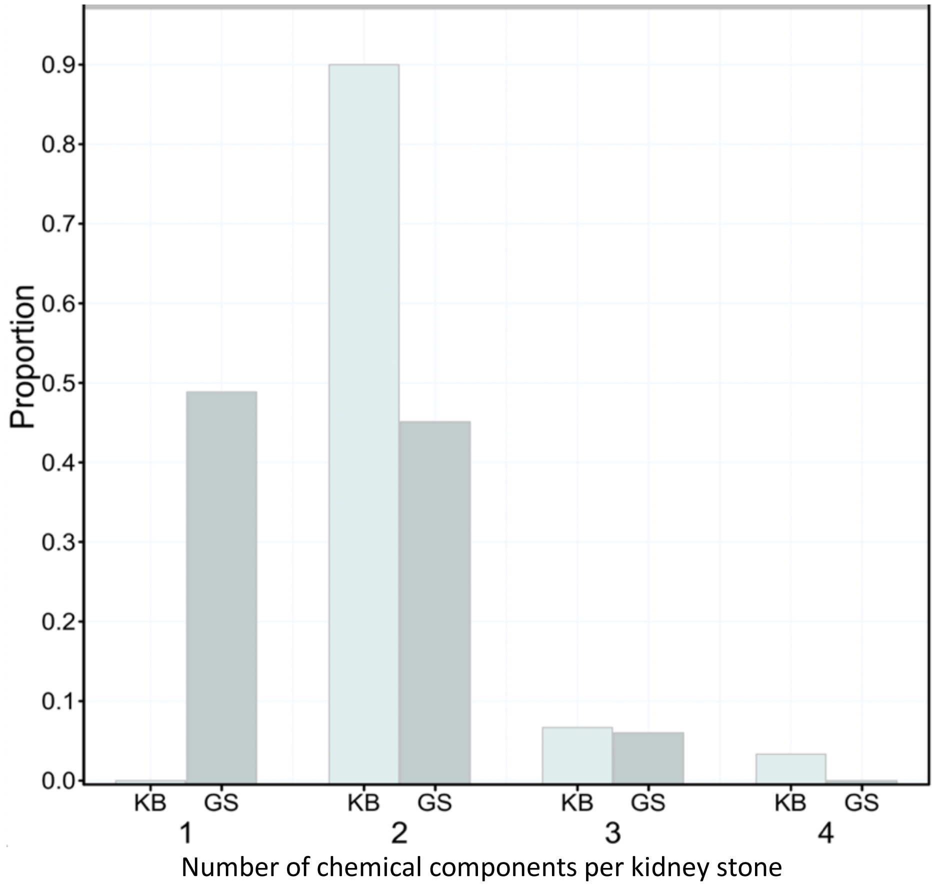

Figure 4.3: Number of chemical components per kidney stone as a function of geographic location (Korle-Bu and Groote Schuur Hospitals) of patients.

4.6 Kidney Stone Classification Analyses

The previous section reported on the prevalence of individual chemical component in the stones examined. In this section, the aim is to classify the kidney stones based on their chemical components. This section grouped stones according to all their chemical components whether they were pure (composed of a single chemical component) or mixed (containing multiple chemical components). The values presented in Table 4.6 were generated to answer these questions.

Table 4.6: Classification of kidney stone as observed among patients treated at Korle-Bu Teaching Hospital and Groote Schuur Hospital

Chemical combinations	**Stone**	**Korle-Bu (n=30)**	**Groote Schuur (n=133)**
Calcium oxalate	Count	***0***	***38***
	Proportion	***0.0000***	***0.2857***
Struvite	Count	***0***	***7***
	Proportion	***0.0000***	***0.0526***
Uric acid	Count	***0***	***18***
	Proportion	***0.0000***	***0.1353***
Other*	Count	0	2
	Proportion	0.0000	0.0150
Calcium oxalate & Carbonate apatite	Count	***0***	***34***
	Proportion	***0.0000***	***0.2556***
Calcium oxalate & Uric acid	Count	***22***	***7***
	Proportion	***0.7333***	***0.0526***
Calcium oxalate & Other*	Count	1	3
	Proportion	0.0333	0.0226
Carbonate apatite & Struvite	Count	***0***	***9***
	Proportion	***0.0000***	***0.0677***
Carbonate apatite & Uric acid	Count	***4***	***0***
	Proportion	***0.1333***	***0.0000***
Carbonate apatite & Other*	Count	0	3
	Proportion	0.0000	0.0226
Struvite & Other*	Count	0	4
	Proportion	0.0000	0.0301
Calcium apatite & Calcium oxalate & Uric acid	Count	1	0
	Proportion	0.0333	0.0000
Calcium apatite & Calcium oxalate & Other*	Count	1	0
	Proportion	0.0333	0.0000
Calcium oxalate & Carbonate apatite & Struvite	Count	0	4
	Proportion	0.0000	0.0301
Calcium oxalate & Carbonate apatite & Uric acid	Count	0	2
	Proportion	0.0000	0.0150
Carbonate apatite & Struvite & Other*	Count	0	2
	Proportion	0.0000	0.0150
Calcium apatite & Calcium oxalate & Carbonate apatite & Other*	Count	1	0
	Proportion	0.0333	0.0000

* Other: Ammonium urate, Brushite, Cystine, Sodium urate monohydrate and Unknown matrix

NB: The bold and italic figures indicate interesting differences in kidney stone chemical component between Groote Schuur Hospital and Korle-Bu Teaching Hospital. Each count is the number of patients whose stones contained only the corresponding chemical combination. The proportions are calculated in terms of the total number of patients from the respective hospitals. That is, n=30 for Korle-Bu and n=133 for Groote Schuur. Bold values indicate combinations with a trend to significant difference between-hospitals.

There are forty-one ($^6_1C + {}^6_2C + {}^6_3C$) possible one (pure/single compound), two and three-component combinations of the six stone classes. Of these, only sixteen were observed at either hospital. Table 4.6 contains all the relevant chemical component combinations for Korle-Bu and Groote Schuur hospitals, including a single four-component stone. The table also contains the counts and proportions (out of the cohort sample size i.e. 30 for Korle-Bu and 133 for Groote Schuur) of patients whose stones had the reported combinations.

In Table 4.6, chemical component combinations that are clinically interesting between the two hospitals are in bold and italic. Clinically interesting observations in the table corresponds to any pair of proportions where the value for one hospital is at least five folds of its analogue at the other hospital. This technique yielded some clinically noteworthy differences for the pure stones and stones made up of two chemical components.

a. As demonstrated in Figure 4.3, there were no pure stones in Korle-Bu patients. The revelations from the pure stone categories at Groote Schuur are that (I.) no stone was made of pure Calcium apatite or Carbonate apatite, and (II.) Calcium oxalate stones (28.57%) are the most common pure stone type.
b. A trend to significance was evident in some two-component mixed stones: Calcium oxalate & Carbonate apatite; Calcium oxalate & Uric acid; Carbonate apatite & Struvite; and Carbonate apatite & Uric acid. Kidney stones composed of a Carbonate apatite & Calcium Oxalate combination or a Carbonate apatite & Struvite combination were identified in Groote Schuur patients exclusively. On the other hand, Carbonate apatite & Uric acid combination stones were only present in the Korle-Bu cohort. While the majority ($22/30$) of the stones examined from Korle-Bu patients were Calcium oxalate & Uric acid combination stones, just a small fraction ($7/133$) of Groote Schuur patients had this type of stone.

Overall, the type of a kidney stone considerably depends on the region (country) from which the patient hails. This is especially true if the stone is pure or made up of two chemical components.

4.7 Kidney Stone Analyses as Function of Demographic Indicators

Considering the sample size constraints, we were cautious in the investigation of demographic indicators to avoid incorrectly inferring significant differences. Consequently, to prevent spurious inferences we partitioned the Age variable into two groups of patients who were (a.) 45 or younger (≤ 45) and (b.) older than 45 (> 45) at the time of examination. The choice of threshold for splitting age was based on the median values in Table 4.3. Interesting differences were instead described as "noteworthy" for further study. Table 4.7, Table 4.8 and Figure 4.6 contain data summarising the Korle-Bu and Groote Schuur data sets with regard to Age and Gender. Despite the limitations of the data size, there are some features of the summaries that are "noteworthy". Thus, in order to minimise the risk of over-mining the data, the following guidelines are adopted to identify "worthy" differences.

Tables 4.7: Number of chemical components per kidney stone of patients treated at Korle-Bu Teaching Hospital and Groote Schuur Hospital as a function of Age and Gender

				Renal Stone Constituent Chemical Count			
				1	**2**	**3**	**4**
Korle-Bu	**Age (year)**	**≤ 45 n=16**	Count	0	15	1	0
			Proportion	0.0000	0.9375	0.0625	0.0000
		> 45 n=14	Count	0	12	1	1
			Proportion	0.0000	0.8571	0.0714	0.0714
	Gender	**Female**	Count	0	10	**2**	1
			Proportion	0.0000	0.7692	**0.1538**	0.0769
		Male	Count	0	17	**0**	0
			Proportion	0.0000	1.0000	**0.0000**	0.0000
Groote Schuur	**Age (year)**	**≤ 45 n=61**	Count	22	36	3	0
			Proportion	0.3607	0.5902	0.0492	0.0000
		> 45 n=72	Count	43	24	5	0
			Proportion	0.5972	0.3333	0.0694	0.0000
	Gender	**Female**	Count	18	29	**7**	0
			Proportion	0.3333	0.5370	**0.1296**	0.0000
		Male	Count	47	31	**1**	0
			Proportion	0.5949	0.3924	**0.0127**	0.0000

*Indicates interesting differences in chemical component of kidney stones **within** hospitals that warrants further studies. Shaded Area indicates interesting differences in chemical component of kidney stones **between** hospitals that warrants further studies*

Table 4.8: Prevalence of chemical components of a kidney stone of patients treated at Korle-Bu Teaching Hospital and Groote Schuur Hospital expressed as a function of Age and Gender

				Renal Stone Chemical Compound Constituent					
				Calcium Apatite	**Calcium Oxalate**	**Carbonate Apatite**	**Struvite**	**Uric Acid**	**Other**
Korle-Bu	**Age (year)**	**≤ 45**	Count	1	16	**0**	0	14	2
			Proportion	0.0625	1.0000	**0.0000**	0.0000	0.8750	0.1250
		> 45	Count	2	10	**5**	0	13	1
			Proportion	0.1429	0.7143	**0.3571**	0.0000	0.9286	0.0714
	Gender	**Female**	Count	**3**	11	3	0	10	**3**
			Proportion	**0.2308**	0.8462	0.2308	0.0000	0.7692	**0.2308**
		Male	Count	**0**	15	2	0	17	**0**
			Proportion	**0.0000**	0.8824	0.1176	0.0000	1.0000	**0.0000**
Groote Schuur	**Age (year)**	**≤ 45**	Count	0	39	30	18	6	10
			Proportion	0.0000	0.6393	0.4918	0.2951	0.0984	0.1639
		> 45	Count	0	49	24	8	21	4
			Proportion	0.0000	0.6806	0.3333	0.1111	0.2917	0.0556
	Gender	**Female**	Count	0	28	32	20	6	**11**
			Proportion	0.0000	0.5185	0.5926	0.3704	0.1111	**0.2037**
		Male	Count	0	60	22	6	21	**3**
			Proportion	0.0000	0.7595	0.2785	0.0759	0.2658	**0.0380**

*Indicates interesting differences in chemical component of kidney stones **within** hospitals that warrants further studies. Shaded Area indicates interesting differences in chemical component of kidney stones **between** hospitals that warrants further studies*

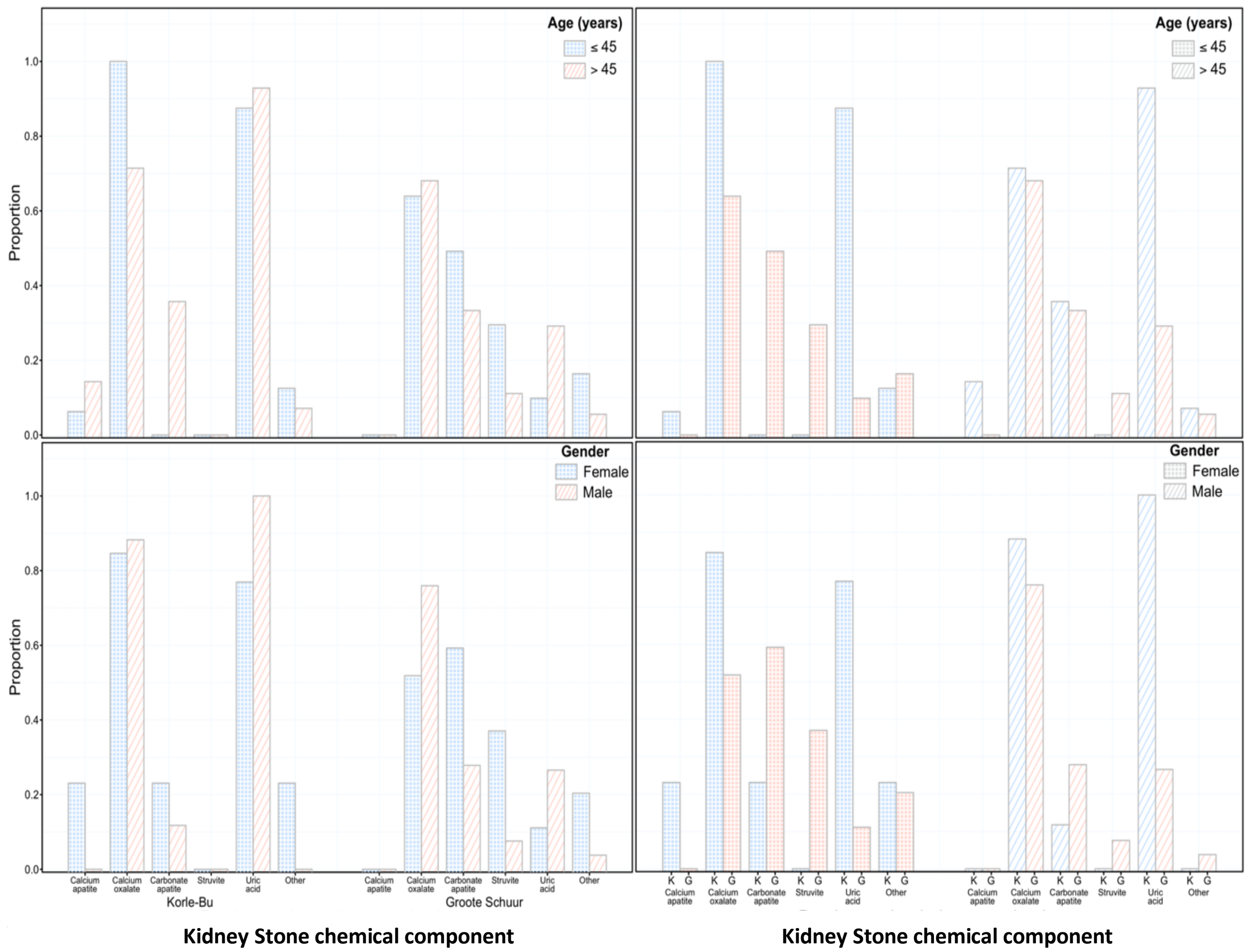

Figure 4.4: Prevalence of chemical component in the kidney stone of patients treated in Korle-Bu (K) and Groote Schuur (G) Hospitals as a function of Age and Gender

NB: The left graphics show within-hospital comparisons, while the right graphics show between-hospital comparisons.

a. For the difference between two values to be considered clinically interesting of future extensive interrogation, at least one of the values must be less than 5% and the other value must be greater than 10%;
b. In addition, given the high magnitude of the weight of a single patient among the Korle-Bu cohort, the difference between a pair of comparative groups need to be at least two patients for such difference to be recommended for future study.

Consequently, the bold values in Tables 4.7 and 4.8 signify interesting differences in chemical component of kidney stones within hospitals that warrants further studies. Shaded Area indicates interesting differences in chemical component of kidney stones between hospitals that warrants further studies. The comments below are thus deductions from the patterns in Figure 4.4 as well as the values in the tables.

a. As expected, given similar inference from Table 4.6, there is notable difference between-hospitals with respect to one-component stones (pure stones). An interesting feature of the demography-diversity interaction is that females tend to have more multi-component (mixed stones). This is more evident in the three-component class among both Korle-Bu and Groote Schuur patients. In fact, while all the male stone formers from Korle-Bu are two components (mixture of two stones), more than 23% $(3/13)$ of the female stone formers have stones containing at least three chemical components and the only four-component stone observed was formed by a female. Also, 60.8% $(48/79)$ of the male stone formers from Groote Schuur formed one component (pure) stones, however, more than 66% $(36/54)$ of the female stone formers from the same hospital formed stones composed of at least two chemical components. Overall, there is clear evidence that, there is no difference in type of stones formed between the age groups provided that the patients are from the same geographic location. There is, however, clear difference in type of stones formed between Korle-Bu and Groote Schuur Hospital.

b. Given the inferences drawn from Table 4.5, the apparent differences in the densities of Calcium apatite and Struvite stones formed by patients from Korle-Bu Teaching Hospital and their counterparts from Groote Schuur Hospital are not unexpected. It is however quite interesting that all Calcium apatite, as well as the *Other* stone category, among Korle-Bu patients are from the females. The *Other* stone category is also evidently common among female patients at Groote Schuur.

c. Another apparent observation (in Table 4.8), is the discrepancy between hospitals in the prevalence of Carbonate apatite for younger (younger than forty-five years) patients. While Carbonate apatite was absent in all the stones from younger patients of Korle-Bu, almost half (48.39%) of their counterparts at Groote Schuur had kidney stones containing a carbonate apatite component. The prevalence of carbonate apatite kidney stones was similar for the older patients (that is, those older that forty-five years old) at both hospitals. All the records of Carbonate apatite in Korle-Bu are interestingly associated with the older patients.

In summary, there are notable differences in the demography and composition of kidney stones between patients from Korle Bu Teaching Hospital and Groote Schuur Hospital.

Chapter Five

5. Discussion of Results

5.1 Introduction

Kidney stone disease is a very debilitating urologic disorder. The results of the study showed no difference in age and gender between the participants from the two hospitals. The results suggest disparities in kidney stone composition among patients depending on the geographic location from where the patient originated. The incidence of kidney stone disease varies with race, ethnicity, geographic location, occupation and diet (López & Hoppe, 2010). Korle-Bu Teaching Hospital (Accra-Ghana) and Groote Schuur Hospital (Cape Town, South Africa) are located in different geographic regions of Africa with different climatic conditions. The ethnicity and diet of individuals of these two countries are also different. With this background knowledge, it is expected that kidney stones from patients of these two countries should vary as illustrated in Figures 4.3 and 4.4. This chapter discusses the results of the study.

Thirty patients from Korle-Bu Teaching Hospital and one hundred and thirty-three patients from Groote Schuur Hospital who were treated for kidney stone disease and had their stones analyzed were included in this study. The male to female ratio from Korle-Bu Hospital dataset was 1.3:1 and that of Groote Schuur Hospital 1.5:1. This study shows a higher prevalence of kidney stone disease in men compared to females in both Korle-Bu and Groote Schuur Hospitals. However, there is no gender diversity among patients treated for urolithiasis in both hospitals. Various epidemiological studies showed male preponderance (Adamu et al., 2015; Bensalah et al., 2008; Scales et al., 2012) which is also confirmed by this study as per the gender characteristics stated above. Some studies have however, reported a higher male-female ratio: 3.5:1 in Nigeria (Ekeke & Okpani, 2018), 2.7:1 in Japan (Hossain et al., 2003b), 3.8:1 in Kenya (Wathigo et al., 2017). The low male-female ratio in this study is thus not surprising. Scales *et al* (Scales et al., 2007) in the United States, using in-patient discharges for kidney stone disease from 1997 to 2002 in their study, observed a dramatic rise in female discharges. This was a demonstration of an increase in the incidence of kidney stone disease in females and therefore, a change in the prevalence of kidney stone disease among men and women from a ratio of 1.7:1 to 1.3:1. This change was attributed to lifestyle changes associated with risk factors such as obesity. This may be the cause of the narrow gender gap observed in this study.

The prevalence of obesity is increasing globally due to dietary and behavioural changes (increased consumption of fast foods, high fructose-containing drinks and increased salt intake) (Romero, Akpinar, & Assimos, 2010).

The median age of patients from the Korle-Bu cohort was 45 years (range 24 to 75) and 48 years (range 19 to 77) for Groote Schuur cohort of patients. The age distribution for both cohorts was similar according to the student t-test ($p = 0.2612$). Kidney stone disease can affect all age groups from as young as 6 months to older than 90 years as was observed by Alaya *et al* (2012) in a retrospective study of 1,301 patients in Tunisia. Notwithstanding the fact that kidney stone disease affects patients of all age groups, it is evident from epidemiological studies that, the peak incidence for this condition occurs between the ages of 20 and 60 years, the most productive age bracket (Bensalah et al., 2008; Phillips et al., 2015; Sofia, Walter, & Sanatorium, 2016; Worster & Supapol, 2012). The median age of patients in this study, is in the 4th decade, with mean ages of 45.13 (± 14.35 SD) and 48.44 (± 14.54 SD) for KBTH and GSH respectively. The median and mean ages observed affirm the results of other studies of the predominance of kidney stone disease in the productive age group. Studies of kidney stone disease in other African countries observed mean ages of 45 years in Nigeria (Ekeke & Okpani, 2018) and 43.5 years in Kenya (Wathigo et al., 2017) suggesting a similar age distribution of kidney stone patients in other African countries compared to this study.

From Figure 4.3, it is evident that kidney stone composition depends on the geographic location of the patient. As illustrated in Tables 4.4 and 4.5 (page 30), calcium oxalate (CaOx) was present in 86.67% of all renal stones from Korle-Bu while only 66.17% contained CaOx in the dataset from Groote Schuur. Uric acid as a component of kidney stone was also present in 90% of all kidney stones in the KBTH dataset, compared with 20.30% in GSH cohort of kidney stones. None of the stones from GSH contained the Hydroxyapatite. Struvite and certain stones from the "Other category" (cystine and brushite) were only found among stones from GSH. Carbonate apatite kidney stones were predominantly present in stones analyzed from GSH (40.60%). Only 16.67% of stones from Korle-Bu contained carbonate apatite.

Ostensibly calcium oxalate is the most prevalent component of all kidney stones from both hospitals. This is not unexpected as calcium oxalate has been found to be the most predominant component, forming 60% to 80%, of all kidney stones globally (Letavernier & Daudon, 2018;

Sakhaee et al., 2012; Tsujihata, 2008). In an Iceland study conducted by Edvardsson *et al.* (2013), they examined recent trends in the incidence of kidney stone disease in adults over a 24 year period, 81% of stones in the study population were CaOx. A similar study in Japan, by Hossain *et al.* (2003) reported CaOx stones in 81.6% of their population. Wathigo *et al.* (2017) also observed 72% in their cohort of patients. Ansari *et al.* (Ansari et al., 2005) reported pure calcium oxalate stones in 93% of their cohort, of which 80% were COM and 20% COD. Calcium oxalate renal stone formation is associated with metabolic anomalies such as hypercalciuria, hypocitraturia, and hyperoxaluria which might be of dietary origin. Other disease conditions such as malabsorption syndromes, primary hyperparathyroidism and distal renal tubular acidosis can cause hypercalciuria or hyperoxaluria with resultant urine supersaturation with these substances. This will eventually culminate in calcium oxalate stone formation. The prevalence of calcium oxalate stones in our cohort is probably related to metabolic abnormalities, but we are unable to confirm the link between metabolic anomaly and stone formation since that was beyond the scope of this study. However, the high prevalence of CaOx component of stones in our study is in keeping with predominance of CaOx stones globally.

Uric acid kidney stones account for about 5% to 10% of all urinary tract stones. However, the incidence varies globally ranging from 5% to 40% depending on the geographic location (Abou-Elela, 2017). It is startling that uric acid was found in 90% of all kidney stones from Korle-Bu. This result should, however, be interpreted with caution due to the small sample size from Korle-Bu. As illustrated from Figure 4.3 (page 32) there were no pure stones among the Korle-Bu cohort. The high proportion of CaOx and UA stones from this dataset suggest CaOx/UA admixed stones. Uric acid stone formation is attributable to low urinary pH ($pH < 5.5$), low urine volume and hyperuricosuria which may be associated with metabolic defect or increase ingestion of purine diet. Korle-Bu (Ghana) is located in the tropics with high daily temperatures and humidity. These conditions obviously will induce profuse sweating with ensuing dehydration and low urine volumes in the absence of adequate fluid intake. These hot and humid weather conditions in tropical countries favour uric acid stone formation as described by some researchers (Abou-Elela, 2017; Sofia et al., 2016). The mechanism by which uric acid and calcium oxalate mixed stones are formed is not absolutely clear, however, the effect of UA on calcium oxalate stone formation is due to UA reducing the solubility of calcium oxalate in urine; a process referred to as salting-out (Abou-Elela, 2017; Xu et al., 2013). A study from Nigeria (country with similar climatic condition to Ghana) did not identify uric acid stone among their sample (Ekeke & Okpani, 2018). This might be due to the fact that, Ekeke *et al* used qualitative chemical analysis to determine stone composition instead of FT-IR spectroscopy. Qualitative chemical analysis of kidney stone has been shown to be beset with many errors in the determination of kidney stone composition. As illustrated from Table 4.5 (page 30), although the proportion of uric acid stones in the GSH dataset is 20.2%, it evident from Table 4.6 (page 33) that two thirds of these stones (13.4%) were of pure uric acid. Pure UA stones are often formed in urine with persistently low pH (pH < 5.5) which is the major risk factor for their formation even in the presence of normouricosuria. Even though hyperuricemia may occur in patients with primary gout, hyperuricosuria does not typically result in pure UA stones formation. This group of, however, can form pure UA stones if their urine is persistently acidic (Abou-Elela, 2017; Daudon et al., 2016; Canales, Doizi, Traxer & Tiselius, 2017). Invariably, pure UA kidney stones are strongly associated with metabolic conditions such as prediabetes, type 2 diabetes and obesity (Chu et al., 2017; Skinner & Sikkema, 2017). These individuals have renal tubular insulin resistance and a defect in renal tubular ammoniagenesis from glutamine with reduced excretion of ammonium to buffer hydrogen ions. The net effect of this process is the production of acidic urine. Conditions which result in excessive loss of bicarbonate in stool such as ileostomy, Crohn's disease, ulcerative colitis and extensive bowel resections especially involving the terminal ileum, may lead to metabolic acidosis and persistent acidic urine production. This may result in UA stone formation. The GSH cohort of patients who formed pure uric acid stones might have conditions associated with persistent acidic urine production, as explained above. Some reseachers (Torricelli et al., 2014) have demonstrated that, uric acid stone formers excrete urine with higher sodium content, lower calcium and lower oxalate contents than CaOx stone formers. Based on these accessions, a multi-centre validation nomogram to predict uric acid kidney stones has been developed using patients' demographic variables (age and BMI) and 24-hour urine parameters (urinary calcium, sodium, oxalate and UA). The nomogram has been assessed to have high accuracy for UA stone formation, with a cutoff of 180 points providing good sensitivity, and using much higher cutoff values yielded higher specificity of the nomogram (Torricelli et al., 2015). Although, we did not assess urine parameters and BMI of stone patients in this study, it is possible pure UA stone patients may be older, have high BMI and excrete urine with high sodium content. This can however, be ascertained in future studies.

From Table 4.4 (page 30) cystine kidney stones constituted about 3.76% of stones from the GSH sample. Of these, 2 were 100% cystine stones. None of the stones analyzed from Korle-Bu contained cystine. Cystine stones are relatively rare, constituting about 1% to 2% of all kidney stones (Chandirika Jayaraman & Gurusamy, 2018; Shima & Parks, 2014). Cystine stones are associated with cystinuria; usually an autosomal recessive hereditary disorder but sometimes heterozygous gene carriers may be autosomal dominant. This condition is associated with impaired reabsorption of cystine by renal tubules, coupled with its relative insolubility in urine which leads to crystallization and cystine stone formation. Cystine stones are often bilateral and have a high recurrence rate (up to 60%) if preventive measures are not adhered to (Shima & Parks, 2014). The rarity of this condition and the small study population from Korle-Bu, might explain the lack of cystine stones in the Korle-Bu cohort. In Nigeria, another West African country, of the eighty-nine stones analyzed in the study by Ekeke *et al* (2018) none were cystine stones. It is plausible that this type of stone might not be found among West African patients. In a study of kidney stone composition involving over 1000 stones from northern India, none of the analyzed stones were cystine (Ansari et al., 2005). This also confirms the rarity of cystine stones. Patients with cystinuria are predisposed to the development of high blood pressure and CKD, hence these patients should be screened for these diseases and treated accordingly. A multi-centre retrospective study in France among 442 cystinuric patients observed a high prevalence of CKD and high BP in the study population. They thus recommended preventive medical treatment and noninvasive urological procedures for these patients to minimize renal damage and also to preserve renal function (Prot-Bertoye et al., 2015).

As per Table 4.4 (page 30), brushite stones were only found among the GSH dataset and constituted 3.01% of all analyzed stones. None of the stones from Korle-Bu were brushite. Calcium phosphate stones exist in three forms: Hydroxyapatite, Brushite and Carbonate apatite. Approximately 15% of all kidney stones are calcium phosphate of which a quarter are brushite stones. Brushite stones are usually the precursor to the formation of Calcium phosphate stones. In the absence of the conversion of Brushite to Hydroxyapatite, brushite stones are formed (Krambeck, Handa, Evan & Lingeman, 2010b; Moreira et al., 2013). The most important risk factors associated with brushite stone formation is hypercalciuria, elevated urine pH and higher supersaturation of urine with calcium phosphate (Krambeck et al., 2010b; Moreira et al., 2013). Brushite stone formation has been strongly linked to the use of ESWL for the treatment of kidney stone disease (Krambeck et al., 2010b). It has been theorized that

ESWL results in destruction of renal tubular cells leading to loss of nephrons' ability to regulate urine pH, with resultant increase in pH of urine (Krambeck, Handa, Evan, & Lingeman, 2010a). Extracorporeal shock wave lithotripsy is common in Cape Town and widely used as a treatment modality for small kidney stones. In Accra, this treatment option is limited or nonexistent. We are unable to tell whether this might explain the zero brushite stones among patients from Korle-Bu. Another likely explanation for the lack of brushite stones is that, at the very extremes of urine pH (i.e. pH <4 or > 8) brushite can spontaneously be converted to Hydroxyapatite stone. Since Hydroxyapatite stones existed among the Korle-Bu dataset, it is possible that conditions (urine pH) might have favoured the conversion of brushite to Hydroxyapatite in the patients from Korle-Bu. Brushite stone formers have a high recurrence rate which often necessitates multiple interventions for stone clearance. It is also evident that brushite stone formers have a higher risk of developing CKD than CaOx patients with prolonged follow up. (Rivera, Jaeger, Yelfimov, & Krambeck, 2017). Brushite stone formers should therefore be monitored closely for CKD to avert progression to ESRD.

Urate kidney stone (ammonium urate and sodium urate monohydrate) components were only found among Korle-Bu patients. Urate stones are usually endemic bladder stones. Beukes *et al.,* (1987) reported a higher prevalence of urate kidney stones among patients of African descent in their study (from South Africa). On the contrary and quite remarkably, our study did not observe any urate component stones among GSH patients.

Struvite, also known as magnesium ammonium phosphate stones, were only found among the GSH cohort constituting 19.55% of all analyzed stone samples. Globally, struvite stones constitute 10 to 15 % of all renal stones. The hallmark of these stones are recurrent urinary tract infections associated with urea splitting organisms as stated in Chapter 2 (Sub-Chapter 2.3 - Risk Factors and Type of Kidney Stones) (page 7). Patients with conditions which predispose them to urinary stasis (urinary tract obstruction, calyceal diverticulum and neurogenic bladder), urinary diversion procedures (continent urinary diversion or ileal conduit), neurologic disorders (spinal injury or pathology), prolonged indwelling urethral catheter and foreign bodies, are inclined to developing recurrent UTI and therefore form struvite stones (Diri & Diri, 2018). Over the past decades, the incidence of struvite stones has been observed to be on the decline in developed countries (Daudon et al., 2016) and this had been attributed to the use of effective antibiotics in the treatment of UTIs. Of the 228 renal stones analyzed from the Iceland study only one of the stones was struvite (Edvardsson et al., 2013). Durgawale *et al.* (2010) however, reported a very high incidence of struvite stones in their series, of which 71.2% of the analyzed stones contained struvite. This is not surprising since they included stones of the lower urinary tract in their work; stones of the lower urinary tract are often associated with infection. Astoundingly, none of the renal stones analyzed from Korle-Bu were struvite. The regulation of antibiotic usage is not strict in Ghana; thus, patients can easily buy antibiotics over the counter for minor ailments. This might have kept the urine of stone-predisposed patients from Korle-Bu sterile, hence preventing recurrent UTIs and struvite stone formation. This is a plausible explanation for the lack of struvite stones in the Korle-Bu dataset. Stone patients from Korle-Bu do not have indwelling double J (DJ) stent for prolonged periods of time before surgery as in GSH patients. This could also be the reason for the lack of struvite stones from Korle-Bu. Intriguingly, Ansari *et al.* (Ansari et al., 2005), in their study of stone composition in northern India, reported 180 (20%) of 1050 observed stones as staghorn calculi. 90% of these staghorn stones were of oxalate composition (calcium oxalate monohydrate and or calcium oxalate dihydrate) while only 4% were composed of struvite. This contravenes the evidence that majority of staghorn kidney stones are of struvite composition.

Carbonate apatite stones constitute about 40.60% of stones from GSH while in Korle-Bu only 16.67% of the stone were of carbonate apatite. This is not as startling as carbonate apatite stones are formed as an extension of the cascade of events that lead to struvite stones formation. The majority of carbonate apatite stones are formed in patients with recurrent UTI and persistently high urine pH. Phosphate is insoluble at high urine pH and under such conditions it easily precipitates out and combines with calcium and carbonate to form carbonate apatite stones. By extension, carbonate apatite stones are considered infection stones and are often associated with struvite stones. They can however, be formed in the absence of struvite stones. A study in the USA assessing the predictability of carbonate content of apatite kidney stones to an underlying infection, revealed that the concentration of carbonate in apatite weakly predicted positive stone culture. However, majority of apatite stones (65%) had positive stone culture results confirming the association of carbonate apatite stones to infection (Nelson & Guyer, 2012).

From Figure 4.3 (page 32) stones analyzed from Korle-Bu were heterogenous or mixed stones made up of at least two or more components. It is therefore not surprising that the only 4 component stone in the dataset came from Korle-Bu. In the GSH dataset 48.87% of the kidney stones were pure stones, and of the mixed stones, the majority of them were of two components (45.11%). The presence of only mixed kidney stones from Korle-Bu may probably be associated with ethnicity, dietary habits and/or climatic conditions prevailing in Ghana. The pure stones in the GSH dataset suggest a possible associated metabolic abnormality in patients who formed such stones. We are unable to link this association in this study, since the metabolic evaluations of patients was beyond the scope of this study.

As illustrated in Table 4.6 (page 33), none of the kidney stones analyzed from the two hospitals were of pure carbonate apatite. This is not extraordinary as carbonate apatite seldomly forms pure stones. A carbonated apatite mixed calcium oxalate stone is often associated with hypercalciuria and relatively alkaline urine in most cases. It may however, also be related to conditions such as medullary sponge kidney or hyperparathyroidism (Cloutier et al., 2014; Daudon et al., 2016). Thus, individuals who present with such stones should be screened to exclude the aforementioned disease entities. Carbonate apatite stones formed in combination with struvite are often associated with urea splitting organisms. Nonetheless, in the absence of struvite, non-urease producing organisms such as *Escherichia coli* are usually the causative organism.

In this study, as illustrated in Table 4.7 (page 35), there is noticeable difference (observed) between gender and stone composition (i.e. pure or mixed). Although, all males from the Korle-Bu cohort formed mixed stones made up of two chemical components, females from both hospitals were predisposed to forming mixed stones with complex heterogeneity (i.e. two or more component stones).

From the data analysis struvite stones were only found among the GSH dataset and shows a high prevalence among females as illustrated in Table 4.8 (page 36) and Figure 4.4 (page 37). This is not unexpected as females are more prone to developing UTI compared with males and hence are more likely to form infection stones (Alelign & Petros, 2018; Diri & Diri, 2018; Ma, Luo, Li, & Zhong, 2018). According to Jayaraman *et al* (2018) for example, globally, the female to male ratio for struvite stone formers is 2:1. This study contrarily revealed a much higher ratio of 3.3:1 (F:M) among GSH cohort than that observed globally. Notwithstanding this difference of no struvite stones in Korle-Bu cohort of patients, this study also confirmed the predominance of struvite stones in female stone formers.

As illustrated in Table 4.8 (page 36) and Figure 4.4 (page 37), carbonate apatite stones were predominantly found in the GSH cohort of patients. While carbonate apatite stones were absent among study participants (less than 45 years old) from Korle-Bu, about 49.18% of the stones from the young patients at GSH were carbonate apatite. This finding is not surprising since these stones are formed in urine with persistently high pH and in association with infection stones (Canales et al., 2017; Nelson & Guyer, 2012; Carpentier *et al.*, 2009) . In this study, struvite stones, which are infection stones, were only found in the GSH cohort of patients. Most of the stone patients in GSH are on urine alkalizing agents (potassium citrate and sodium citrate) which can keep the pH of urine persistently high (if urine pH is not closely monitored) thereby encouraging carbonate apatite stone formation. Another likely explanation for this phenomenon is that patients from GSH often have double J (DJ) stents in-situ to decompress an obstructed system for a number of months while waiting for their surgeries (due to the long waiting time). These patients often have their DJ stents exchanged biannually and may have stent changes two or three times before they are due for surgery. These stents are likely to get colonized by urease producing bacteria which will consequentially keep the urine perpetually alkalized and hence foster formation of infection stones (carbonate apatite and struvite). Carbonate apatite stones from this study were predominantly found in female stone formers in the two hospitals. This is not unexpected since females are more predisposed to urinary tract infection compared with their male counterparts. Other researchers have also reported a greater prevalence of carbonate apatite kidney stones in females than men (for example, Ma *et al.*, 2018; Carpentier *et al.*, 2009).

Although no patient from Korle-Bu formed pure stones, females from both hospitals formed more complex heterogenous (mixed) kidney stones than males as shown in Table 4.7 (page 35). It is evident from this study that kidney stone composition in females is different from that in men. The category of stones labelled as *Other* were mostly stones formed by females from both hospitals. A study from Mayor Clinic Metal Laboratory in USA reported that over 43,500 of the kidney stones analyzed showed gender variations in stone composition. Females were found to form more apatite (calcium phosphate) and struvite stones while men were prone to forming CaOx and uric acid stones (Lieske *et al*., 2014). In the same study, Lieske *et al.,* (*ibid*) also observed that females, particularly younger than 40 years, predominantly formed apatite kidney stones. Our study also confirmed that apatite stones were largely found among female stone formers as illustrated in Figure 4.4 (page 37). On the contrary, Wathigo *et al.* (2017) in

Kenya and Ansari *et al.* (2005) in India did not observe any gender disparity of stone composition in their study.

There is evidence that the incidence of kidney stone disease increases with increasing age and also varies with age stratification as observed in some epidemiological studies (Romero et al., 2010). Although, our study stratified age of the cohort of patients into less or equal to 45 years and greater than 45 years, we did not study the incidence of stone disease in these patients. On the whole, the analysis of kidney stone composition among our cohort of patients did not vary between the age groups provided the patients came from the same geographic location. The observation of no difference in stone composition regardless of age has also been reported by other researchers in other countries where kidney stone compositional studies have been conducted (Wathigo et al., 2017; Ansari et al., 2005; Lieske et al., 2014).

A study conducted in the late 1980s by Beukes et al., (1987) on composition and racial distribution of kidney stones from Bloemfontein, South Africa, observed the predominance of CaOx stones among the racial groups studied. This observation is confirmed by this current study that calcium oxalate stones are the most common stone type as seen among patients from Ghana (mainly African descent) and South Africa (mixed race) although race was not directly a subject matter in our study. Beukes *et al* (1987), observed a higher proportion of struvite and ammonium urate stones (infection stones) among the patients of African descent in their patient population at the time. Contrary to their observation none of the patients from Ghana had struvite stones. We are unable to confirm in this study whether the infection stones among the South African cohort were more common in a particular race as race stratification was not considered in the study. A sub-analysis of the data might be able to ascertain the veracity of this accession as to whether the disease pattern has changed among the South African population.

5.2 Summary of Discussion

In summary there were no differences in age or gender distribution between the Ghanaian and South African stone patients. Pure kidney stones (CaOx, UA, Cystine and Struvite) and struvite admixed stones were only found in GSH dataset. All kidney stones from Korle-Bu were of mixed composition. Carbonate apatite, struvite and Other category stones as well as multi-component stones were commonly found among female patients in both Hospital. This study demonstrated that, the variation in kidney stone composition is dependent on the geographic location of the patient. There is also gender variation regards kidney stone composition between Ghana and South Africa.

This study has some limitations; the small sample size of kidney stone patients especially from Korle-Bu precludes very meaningful statistical comparison of data from the two hospitals. This limitation thus restricts the study to mostly descriptive analysis. A convenient sampling method was used due to the small size of the sampling frame which constrained randomization of the study and generalization of the results to the population. This study also did not include parameters such as metabolic anomalies and urine studies that are associated with kidney stone formation. This might have been relevant in showing significant similarities and/or differences between the study population (for example, the racial diversity in South Africa and its impact on the characteristics of kidney stone). Due to these limitations the results and conclusions (especially of statistical inferences) should be interpreted with caution. Notwithstanding these limitations, this study is very relevant as a guide to extensive future studies on kidney stone disease between countries, where a larger sample exists.

Chapter Six

6. Conclusion and Recommendation

6.1 Conclusions

The analyses discussed in this study are based on samples from Korle-Bu Teaching Hospital (Accra, Ghana) and Groote Schuur Hospital (Cape Town, South Africa). Both hospitals are open to the public and offer a variety of services to their patients. It can therefore be conservatively assumed that the patients treated at both hospitals are representative of the population of their respective countries. Thus, without loss of the rules of generality, the inferences presented in this section are loosely extended to the population of Ghanaian and South African renal stone patients.

This study sought to describe the demography and kidney stone composition among patient who were treated for kidney stone disease at Korle-Bu teaching Hospital and Groote Schuur Hospital, and also compare the results between the two hospitals. The study has adequately described the age and gender distributions and kidney stone composition of patients treated in the two hospitals as elaborated in chapter four. The comparative analysis of demography and kidney stone composition has also been clearly described in Chapter four.

The study shows similar gender distribution of kidney stone patients who were treated in Korle-Bu and Groote Schuur hospital. There is also no significant difference in age distribution of patients who were treated for stone disease in both hospitals from Ghana and South Africa. Majority of the kidney stones from both countries were made up of calcium oxalate. All stones from the Ghanaian cohort were mixed stones of which majority were an admixed of calcium oxalate/uric acid composition. Pure kidney stones such as calcium oxalate, uric acid, struvite and cystine were only present among the South African cohort of patients. Although some patients from Ghana formed carbonate apatite stones, most stones with this component in this study were predominantly formed by South African patients. Certain kidney stone types, especially brushite, cystine and struvite were only found among the South African population, while Calcium apatite and ammonium urate components stone were found in kidney stones from Ghanaian patients. Carbonate apatite and stones with multiple components (mixed stones) were predominantly formed by female patients from both countries. Notwithstanding the small data especially from Ghana, it is noteworthy to infer from this study that kidney stone composition in Ghana is different from South Africa, therefore the composition of kidney stone is recognizably dependent on the demographic region from which the patient originates.

6.2 Future Study

The analyses presented in this study is based on quite a few observations. There are many aspects that this work could benefit from further observation. The accuracy of the generalization of the inferences made is likely to benefit from more representative observations from across both Ghana and South Africa. Analyses of the South African data in this report ignored the racial diversity of the country which could be an interesting factor in understanding stone formation among diverse races of African descent or origin. A sub-analysis based on a larger dataset is necessary to investigate racial effects on kidney stone compositions and whether the result of such study will affect current treatment protocol. Since diet has been implicated as a risk factor to stone disease, and diet also varies with ethnicity, it would be enthralling to study the diet composition of the Ghanaian and South African stone patients to ascertain the link between diet and stones formed in the two geographic regions. A study of metabolic risk factors, 24-hour urine study as well as comorbidities (like DM and obesity) of these patients in the future may establish the contributing factors to stone formation. Further work involving urinalysis and urine culture studies may reveal the organisms that were responsible for infection stones. This may also in part answer the question of there are no struvite stones among the Ghanaian patients. It is imperative to subdivide calcium oxalate stones into calcium oxalate monohydrate and calcium oxalate dihydrate since both are associated with different metabolic anomalies.

All the analyses in this study were based on the patient counts as is the tradition in the literature (see for example, Wathigo, et al. 2017 and Hossain, et al. 2003a). Records of the percentage chemical component of kidney stones were ignored. With larger data sets, analyses of the percentage compositions based on compositional data analysis (Jones & Aitchison, 2006) may yield novel insights and consequently lead to more effective renal stone diagnosis and treatment techniques.

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Appendices

Appendix 1: Datasheet

DEMOGRAPHY | TYPE OF STONE

Folder Number: ☐☐☐☐☐☐☐☐☐☐☐☐

A. DEMOGRAPHY

1. Country of Origin: South Africa ☐ Ghana ☐
2. Date of Surgery ☐☐☐☐☐☐ (D D M M Y Y) Stone Analysis Date ☐☐☐☐☐☐ (D D M M Y Y)
3. Gender: Male ☐ Female ☐ Age: ☐☐

4. Employment Status Employed Unemployed

(It was later discovered from the data that respondents either stated their employment status or didn't. All the declared statuses were stated as employed however, since the employment status of the undeclared population is unknown, it was left as "undeclared" in the employment status classification)

B. STONE COMPONENTS

4. Calcium oxalate monohydrate ____% ☐
5. Calcium oxalate dihydrate ____% ☐
6. Calcium phosphate ____% ☐
7. Struvite ____% ☐
8. Uric acid ____% ☐
9. Cysteine ____% ☐
10. Ammonium urate ____% ☐
11. Brushite ____% ☐
12. Other ____% ☐

Appendix 2: Ethics Approval (University of Cape Town)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 September 2018

HREC REF: 601/2018

Dr L Kaestner
Urology
Surgery
E26, NGSH

Dear Dr Kaestner

PROJECT TITLE: COMPARATIVE ANALYSIS OF KIDNEY STONE COMPOSITION IN PATIENTS OF TWO DEVELOPING COUNTRIES, GHANA AND SOUTH AFRICA: CASE STUDY OF RENAL STONES FROM ACCRA AND CAPE TOWN (MSc Candidate – Dr E Akpakli)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to approval from the Ghana Ethics Committee.

Approval is granted for one year until the 30 September 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

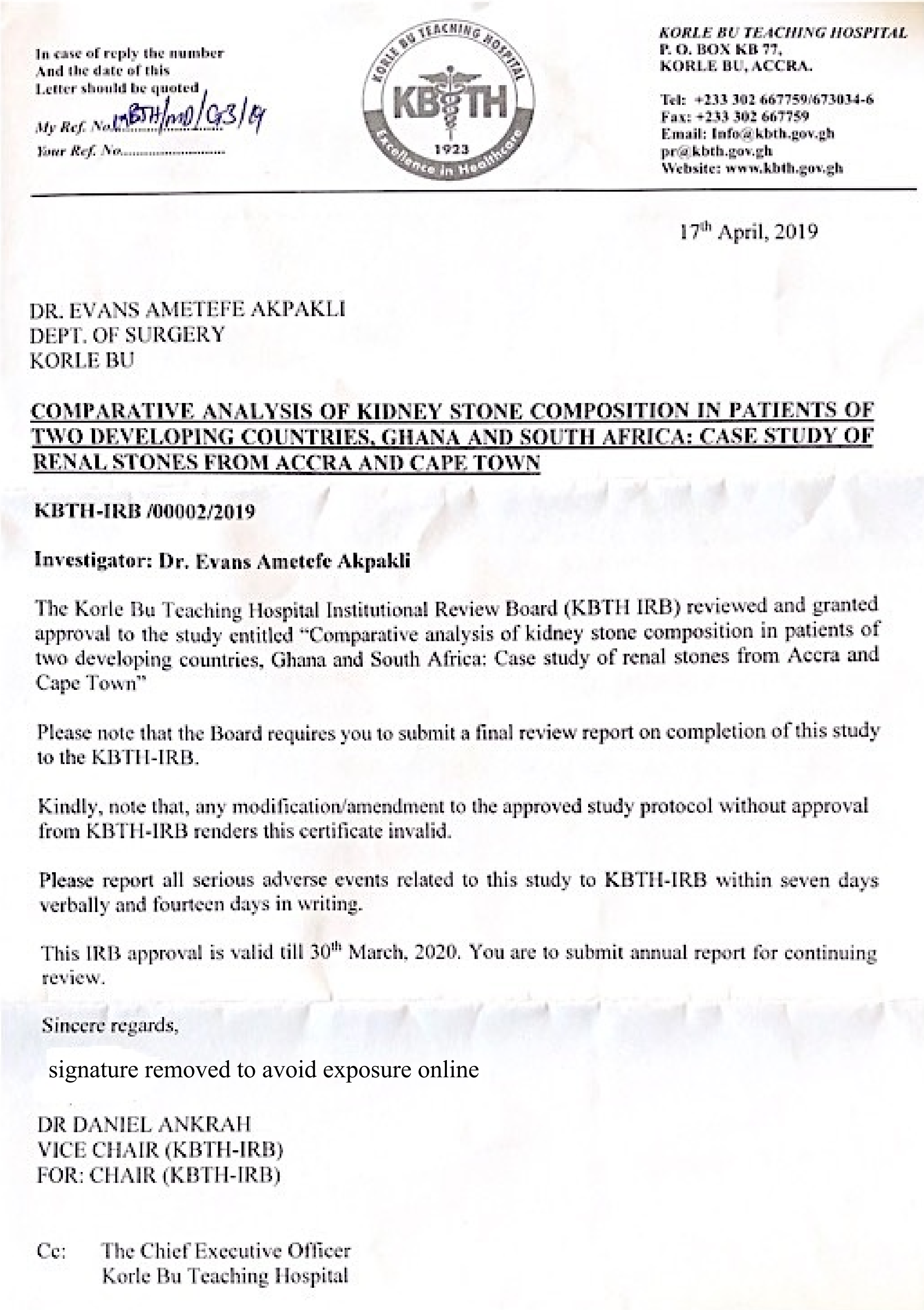
The HREC acknowledge that the student, Dr Evans Akpakli will also be involved in this study.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

Appendix 3: Ethics Approval (Korle-Bu Teaching Hospital)



In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/IRB/03/19
Your Ref. No...........................

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17th April, 2019

DR. EVANS AMETEFE AKPAKLI
DEPT. OF SURGERY
KORLE BU

COMPARATIVE ANALYSIS OF KIDNEY STONE COMPOSITION IN PATIENTS OF TWO DEVELOPING COUNTRIES, GHANA AND SOUTH AFRICA: CASE STUDY OF RENAL STONES FROM ACCRA AND CAPE TOWN

KBTH-IRB /00002/2019

Investigator: Dr. Evans Ametefe Akpakli

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled "Comparative analysis of kidney stone composition in patients of two developing countries, Ghana and South Africa: Case study of renal stones from Accra and Cape Town"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th March, 2020. You are to submit annual report for continuing review.

Sincere regards,

signature removed to avoid exposure online

DR DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB)

Cc: The Chief Executive Officer
Korle Bu Teaching Hospital