

A Review of Patterns of Renal Disease at Chris Hani Baragwanath Academic Hospital from 1982 to 2011

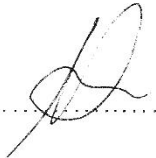
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Internal Medicine.

Johannesburg, 2014

DECLARATION

I, Alda Vermeulen, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: 

Date: 12th day of April 2014

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

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ABSTRACT

This study reports a review of biopsy-confirmed renal pathology from Soweto Gauteng.

A retrospective analysis was conducted of 1848 adult native renal biopsy reports from Chris Hani Baragwanath Academic Hospital from 1 January 1982 to 31 December 2011.

The mean age of all patients biopsied was 33.5 ± 12.6 years and the majority of patients (96.4%) were black. The most frequent histological findings were secondary glomerular diseases (SGNs) (49.3%) and primary glomerular diseases (PGNs) (39.7%). SGNs increased, while PGNs decreased over time ($p < 0.001$). The main contributors to SGN were lupus nephritis (31.0%) and HIV associated nephropathy (HIVAN) (13.3%) while for PGN it was focal segmental glomerulosclerosis (FSGS) (29.6%). HIV positive biopsies constituted 19.7% of all biopsies with a dominant diagnosis of HIVAN (32.7%).

Changing patterns of renal disease are evident in the data. The increased SGNs likely reflect the influence of renal pathology secondary to HIV and lupus nephritis.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney injury
AMY	Amyloidosis
ANA	Anti-nuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
APOL1	Apolipoprotein L1 gene
ARV	Antiretroviral therapy
ASOT	Anti-streptolysin O titre
ATIN	Acute tubulointerstitial nephritis
ATN	Acute tubular necrosis
AUA	Asymptomatic urine abnormalities
BHN	Benign hypertensive nephroangiosclerosis
C3	Complement factor 3
CD4	Cluster of differentiation 4
DDD	Dense deposit disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CKD	Chronic kidney disease
CresGN	Crescentic glomerulonephritis
DN	Diabetic Nephropathy

EM	Electron microscopy
ESRD	End stage renal disease
Fibrillary GN	Fibrillary glomerulonephritis
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GPA	Granulomatosis with polyangiitis / Wegener's granulomatosis
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HELLP	Haemolysis elevated liver enzymes low platelet syndrome
HIV	Human Immunodeficiency Virus
HIVAN	Human Immunodeficiency Virus associated Nephropathy
HIV-ICD	Human Immunodeficiency Virus Immune complex disease
H	Haematuria
HR	Hereditary diseases
HT	Hypertension
ID	Infectious diseases
IFTA	Interstitial fibrosis and tubular atrophy
IgAN	Immunoglobulin A nephropathy
IgG	Immunoglobulin G
IgM	Immunoglobulin M nephropathy

IMF	Immunofluorescence
Immunotactoid GN	Immunotactoid glomerulonephritis
ISN/RPS	International Society of Nephrology / Renal Pathology Society
IN	Interstitial nephritis
KDIGO	Kidney disease improving global outcomes
KZN	Kwazulu-Natal
LM	Light microscopy
MCD	Minimal change disease
MD	Metabolic and deposit disease
MGN	Membranous glomerulopathy / glomerulonephritis
MHN	Malignant hypertensive nephroangiosclerosis
MPGN	Membranoproliferative glomerulonephritis / Mesangiocapillary glomerulonephritis
MsPGN	Mesangioproliferative glomerulonephritis
NS	Nephrotic syndrome
N	Nephritic syndrome
NN	Nephritic nephrotic syndrome
NHLS	National Health Laboratory Service
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Protein-creatinine ratio

PET	Pre-eclamptic toxemia
PGN	Primary glomerular disease
PIGN	Post infectious glomerulonephritis
PLA ₂ R1	M-type Phospholipase A2-receptor
ProlifGN	Proliferative glomerulonephritis
SADTR	South African dialysis and transplant registry
SD	Systemic diseases
SGN	Secondary glomerular disease
SLE	Systemic lupus erythematosus
suPAR	Soluble urokinase plasminogen activating receptor
TID	Tubulointerstitial diseases
TMA	Thrombotic microangiopathy
TU	Tumours
USA	United States of America
USRDS	United States Renal Data System
VD	Vascular diseases

1. INTRODUCTION

1.1 Background and History

Studies suggest that there is marked variation geographically and temporally in renal disease patterns (Sliem, *et al.*, 2011), but fairly limited data is available regarding patterns of renal disease in Africa (Okpechi, *et al.*, 2012).

According to the 2012 United States Renal Data System (USRDS), diabetes, hypertension and glomerulonephritis are the three major contributors to end stage renal disease (ESRD) in the United States of America (USA), accounting for 37%, 25% and 14% respectively of ESRD. Glomerular diseases, which consist of a broad spectrum of clinicopathological syndromes – including glomerulonephritis, account for 90% of ESRD at a cost of \$20 billion per year in the USA (Wiggins, 2007). Even though there is a lack of available registries in sub-Saharan Africa, chronic kidney disease (CKD) seems to be 3-4 times more frequent in developing countries (Naicker, 2009).

From available data it appears that glomerular disease is more prevalent in developing countries like South Africa; where patients have a poorer response to therapy and a greater rate of progression to ESRD in areas where renal replacement therapy is limited (Naicker, 2010).

According to Katz, *et al* (2007) in a Soweto based chronic disease outreach programme that assessed 619 high risk diabetics (diabetics with hypertension or proteinuria) and uncontrolled hypertensive patients, 12% of patients were found to have CKD with a glomerular filtration rate (GFR) of $<60\text{ml/min/1.73m}^2$.

The 1994 South African Dialysis and Transplant Registry (SADTR) reported glomerulonephritis to be the cause of ESRD in 52.1% and hypertension in 45.6% of patients (Naicker, 2003). Gold, *et al* (1982) reported the most frequent cause of ESRD on biopsy at Chris Hani Baragwanath Academic Hospital (CHBAH) between October 1972 and December 1976 to be malignant hypertension (49%) which occurred with a male predominance, followed by chronic glomerulonephritis (40%).

More recent data from Nigeria found the top three causes of ESRD to be chronic glomerulopathy (45.6%), hypertensive nephropathy (29.7%) and diabetic nephropathy (DN) (17.5%) (Alasia, *et al.*, 2012).

1.2. Clinical Presentation of Renal Disease

Renal disease may be asymptomatic and detected with screening or present with features related to renal dysfunction or with signs and symptoms related to an underlying systemic disease (Floege & Feehally, 2010). The presentation of the specific renal disease often depends on the underlying aetiology of renal disease.

Nephrotic syndrome (NS) is one of the best known presentations of glomerular disease and is defined as the presence of proteinuria of >3.5g per day occurring in association with hypoalbuminaemia, peripheral oedema and hyperlipidaemia (Hull & Goldsmith, 2008).

According to Nachman, *et al* (2012) NS can be caused by primary glomerular diseases including:

1. Focal segmental glomerulosclerosis (FSGS)
2. Membranous glomerulonephritis / glomerulopathy (MGN)
3. Minimal change glomerular disease (MCD)
4. Mesangioproliferative glomerulonephritis (MsPGN)
5. Membranoproliferative glomerulonephritis (MPGN)
6. Fibrillary glomerulonephritis (Fibrillary GN)
7. Immunotactoid glomerulopathy (Immunotactoid GN)

The most frequent causes of NS in adults found on analysis of 9605 renal biopsies in North Carolina were MGN and FSGS with MGN having a higher frequency in white patients than in black patients (Nachman, *et al.*, 2012).

MCD accounts for 10-15% of NS in adults (Waldman, *et al.*, 2007).

In a retrospective study in Cape Town South Africa of biopsies from 294 black patients with NS the most common cause was found to be human immunodeficiency virus associated nephropathy (HIVAN) and the most frequent primary glomerular disease (PGN) causing NS was MPGN (Okpechi, *et al.*, 2010).

NS may also occur secondary to exposure to drugs and toxins, infectious agents, neoplasms, multisystem illnesses, hereditary and metabolic diseases (Floege & Feehally, 2010).

According to Floege & Feehally (2010) glomerular disease may also be asymptomatic with proteinuria between 150-3000mg per day or seen as glomerular (usually dysmorphic red blood cells) haematuria or present with nephritic syndrome characterized by abrupt onset of oliguria, haematuria,

proteinuria (usually subnephrotic), oedema and hypertension; macroscopic haematuria (usually with intercurrent infection); rapidly progressive glomerulonephritis with renal dysfunction developing over days/weeks, proteinuria and haematuria or as a chronic glomerulonephritis with small shrunken kidneys, hypertension, proteinuria > 3g per day and renal insufficiency.

Nephritic syndrome is most frequently caused by proliferative glomerulonephritis, MPGN and crescentic glomerulonephritis (Nachman, *et al.*, 2012).

Haematuria is usually defined as the presence of > 3 red blood cells per high power field seen with microscopy of a centrifuged urine specimen. Asymptomatic microscopic haematuria occurs in 5-10% of the general population and <10% of isolated haematuria is caused by glomerular disease (Jennette & Falk, 2009).

Renal disease can present as acute kidney injury (AKI) or CKD. Kidney disease improving global outcomes (KDIGO) workgroups for AKI (2012) and CKD (2013) define AKI as either an increase in serum creatinine of $\geq 26.5 \mu\text{mol/l}$ within 48 hours, an increase in serum creatinine to ≥ 1.5 times the baseline creatinine (taken within the prior 7 days) or a urine volume of $< 0.5\text{ml/h}$ for 6 hours and CKD as abnormalities of kidney structure or function with markers of kidney damage (albuminuria $\geq 30\text{mg/24h}$, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, histological abnormalities, structural abnormalities on imaging or a history of renal transplantation) or a GFR $< 60\text{ml/min/1.73m}^2$ present for > 3 months, with implications for health.

A broader definition of AKI is the presence of a rapid deterioration of the GFR over hours to days with resultant retention of metabolic waste products including

urea and creatinine with an associated dysregulation in the homeostasis of electrolytes, acid-base and fluid balance (Sharfuddin, *et al.*, 2012).

AKI is a heterogeneous condition with a wide spectrum of causes that are generally divided into (Sharfuddin, *et al.*, 2012):

1. pre-renal causes with effective renal hypoperfusion
2. intra-renal causes by diseases involving large or small blood vessels and glomeruli, ischaemic or nephrotoxic acute tubular necrosis (ATN)
3. diseases of the tubulointerstitium and post renal causes

According to the KDIGO guidelines AKI can be divided into the following 3 stages:

1. Stage 1: 1.5-1.9 times increase from baseline creatinine or $\geq 26.5 \mu\text{mol/l}$ increase in creatinine or a urine output of $< 0.5 \text{ ml/kg/h}$ for 6-12 hours.
2. Stage 2: 2.0-2.9 times increase from baseline creatinine or a urine output of $< 0.5 \text{ ml/kg/h} \geq 12$ hours.
3. Stage 3: 3.0 times increase from baseline creatinine or a creatinine $\geq 353.6 \mu\text{mol/l}$ in or a urine output of $< 0.3 \text{ ml/kg/h}$ for ≥ 24 hours or anuria for ≥ 12 hours.

In Africa patients often present late with an abnormal creatinine making it difficult to distinguish between AKI and CKD, therefore in some local studies (Okpechi, *et al.*, 2011) patients are labelled as having CKD if they have a persistently raised serum creatinine for more than 3 more months or if they presented with an elevated serum creatinine in association with a low haemoglobin and echogenic kidneys on renal ultrasound.

KDIGO classifies CKD according to the level of GFR, the amount of albuminuria and cause of CKD.

The categories of CKD as defined by GFR include:

1. CKD stage 1: $\text{GFR} > 90 \text{ ml/min/1.73 m}^2$
2. CKD stage 2: $\text{GFR } 60\text{-}89 \text{ ml/min/1.73 m}^2$
3. CKD stage 3: $\text{GFR } 30\text{-}59 \text{ ml/min/1.73 m}^2$
4. CKD stage 4: $\text{GFR } 15\text{-}29 \text{ ml/min/1.73 m}^2$
5. CKD stage 5: $\text{GFR} < 15 \text{ ml/min/1.73 m}^2$

1.3 Diagnosing Renal Disease

Renal biopsy is the main method for making a definitive diagnosis of renal disease (Schena & Gesualdo, 2004). On histopathological examination of a renal biopsy specimen the injury localization can be made to be glomerular, vascular or to the tubulointerstitium (Fogo, 2003). According to Howie (2008) the aim of the renal biopsy is to establish a diagnosis that will aid in establishing chronicity of the disease, predicting the likely clinical course, further investigations and management of the patient.

The first prone transcutaneous renal biopsy was performed in 1954 by Kark and Meuhrcke using a Vim-Silverman needle, since then the procedure has advanced to where the Tru-cut needle, spring-loaded automatic and semi-automatic biopsy guns are used under ultrasound guidance by most nephrologist these days. Other biopsy routes include laparoscopic, transjugular and open renal biopsy for more complicated patients (Agarwal, *et al.*, 2013).

The major indications for native renal biopsy include (Topham & Chen, 2010):

1. NS
2. AKI
3. Systemic diseases with renal dysfunction
4. Non nephrotic proteinuria
5. Isolated microscopic haematuria
6. Unexplained CKD
7. Familial renal disease

Contra-indications for performance of transcutaneous renal biopsy can be absolute contraindications including, widespread cystic or malignant disease, bleeding diathesis, uncontrolled hypertension, an uncooperative patient or patient refusal, and hydronephrosis. Relative contraindications for transcutaneous renal biopsy include a solitary kidney or anatomic abnormalities, small kidneys, patient use of antiplatelet and anticoagulant therapy, active urinary and skin sepsis and inability of the patient to lie flat (Salama & Cook, 2012).

Complications of renal biopsies occur more frequently in patients with more severe renal dysfunction, bleeding diathesis, lower haemoglobin levels and uncontrolled hypertension (Salama & Cook, 2012).

According to Whittier (2012) complications can be divided into major complications needing interventions or minor complications that resolve spontaneously. Gross haematuria occurs in 3-18% of biopsies with only 1-6% of patient's requiring transfusions for bleeding or haematomas. Around 0.1-0.4% of

patients will require an intervention to stop bleeding or a nephrectomy with death occurring rarely in 0.02-0.1% of percutaneous kidney biopsies.

The number of glomeruli present in a biopsy specimen to make it adequate for a diagnosis of a glomerular disease is 5 glomeruli and 7-10 glomeruli for tubulointerstitial diseases (TID) (Agarwal, *et al.*, 2013).

Biopsy specimens are generally examined under light microscopy (LM) after special staining with stains like Haematoxylin and Eosin stain and Periodic Acid-Schiff stain and under immunofluorescence (IMF) to localize immune deposits by using an unfixed frozen specimen with addition of Fluorescein labelled antibodies. For ultra-structural examination electron microscopy (EM) is performed to help localize deposits and view structural changes in the glomerular basement membrane and cells (Agarwal, *et al.*, 2013).

1.4 Renal Disease Classification

Renal disease classification is based on the histological involvement of the various components of the kidney in a variety of patterns.

At a basic level the major functional components of the kidney are the nephron which consists of the glomerulus (renal corpuscle) and a tubular component with its interstitium, the collecting ducts and a unique microvasculature (Kriz & Elger, 2010).

The renal corpuscle consists of a tuft of glomerular capillaries lined by endothelial cells and their basement membrane, a central mesangial region (consisting of cells and matrix), Bowman's space (urinary space) lined by visceral epithelium (podocytes) and parietal epithelial cells with their basement membrane

and the glomerular basement membrane that is formed by fusion of the endothelial and visceral epithelial basement membranes during development (Nielsen, *et al.*, 2012).

Renal disease may follow direct disease or damage and/or general systemic involvement of any of these components individually or combined. Renal disease may start in the tubulointerstitium, glomeruli or renovasculature due to systemic illnesses like autoimmune reactions, diabetes, hypertension, drugs and toxins, infections, mechanical damage, obstruction of the urinary tract, ischaemia, primary genetic abnormalities or idiopathic causes (López-Novoa, *et al.*, 2011).

Regardless of whether the renal injury started in the glomeruli, tubulointerstitium or renovasculature the chronic progression finally converges to cause generalized and progressive fibrosis and glomerulosclerosis on histology with associated functional changes in most of the kidney components (López-Novoa, *et al.*, 2011).

1.4.1 Glomerular diseases

Glomerular disease encompass a broad group of diseases in which the structure and function of glomeruli are altered by conditions that primarily affect the glomerulus (primary glomerular diseases – (PGNs)) or due to involvement of the glomerulus by a systemic disease (secondary glomerular diseases – (SGNs)) (Nachman, *et al.*, 2012). The clinical presentation and pathologic findings of SGNs may mirror that of PGNs.

Because the underlying molecular basis for most primary glomerulonephritides is still largely unknown the PGNs are classified according to their histological pattern (Jiang, *et al.*, 2013).

MCD and FSGS are caused by changes in the shape of the podocytes with rearrangement in the actin cytoskeleton with resultant loss of the integrity of the glomerular filtration barrier. This process is potentially reversible in MCD but progressive in FSGS (D'Agati, *et al.*, 2011). Recently, soluble urokinase plasminogen activating receptor (suPAR) was identified as a factor involved in the pathogenesis of primary FSGS due to its effect on the actin cytoskeleton (Schell & Huber, 2012).

MCD is defined by the absence of glomerular abnormalities on LM with evidence of podocyte foot process fusion (effacement) on ultra-structural examination – EM (Mason & Hoyer, 2010). MCD causes 10-25% of NS in adults of which 20-25% may have AKI at presentation.

Most cases of MCD are idiopathic but secondary causes should be excluded in adults. Secondary causes of MCD includes: drugs (non-steroidal anti-inflammatory drugs (NSAIDs), lithium, enalapril, and rifampicin), malignancies (Hodgkin's lymphoma and solid tumours), infections (syphilis, echinococcus, human immunodeficiency virus (HIV) and mycoplasma), atopy (allergic stimuli e.g. food and dust) and systemic lupus erythematosus (SLE) (Hogan & Radhakrishnan, 2013; Becker, 2008; Nachman, *et al.*, 2012).

FSGS accounts for about 40% of NS in adults at an estimated incidence of 7 per million population with 50-60% of adults with FSGS presenting with NS (D'Agati, *et al.*, 2011). FSGS can be idiopathic (primary) – 80% of cases, adaptive

(mediated by glomerular hypertension and hyperfiltration), genetic (inherited mutations of specific podocyte genes) or secondary to a variety of viruses (HIV1, Parvovirus B19, Simian virus 40, cytomegalovirus and Epstein-Barr virus) and drugs (heroin, interferon's alpha, beta and gamma, lithium, pamidronate, sirolimus, calcineurin inhibitor nephrotoxicity and anabolic steroids) (D'Agati, *et al.*, 2011).

On LM FSGS is seen as a focal segmental glomerulosclerosis starting with consolidation of glomeruli with entrapment of plasma proteins with several sub-types with various prognostic implications. Morphological sub-types include the tip, perihilar, cellular and collapsing variants and FSGS not otherwise specified (Jiang, *et al.*, 2013; D'Agati *et al.*, 2011). On EM examination extensive foot process effacement is seen without other glomerular basement membrane abnormalities (Jiang, *et al.*, 2013; D'Agati *et al.*, 2011; Nachman *et al.*, 2012).

African patients have a 3-4 times higher risk to develop FSGS and HIVAN with an associated risk of more rapid progression and poorer prognosis due to the presence of coding sequence variants (G1 and G2) within the apolipoprotein L1 (APOL1) gene, which is also associated with a higher risk of developing non-diabetic ESRD in these individuals (Schell & Huber, 2012; Papeta, *et al.*, 2011; D'Agati, *et al.*, 2011).

MGN is the cause of NS in about 25% of adults (Nachman *et al.*, 2012). MGN can be primary (70% of patients) or secondary. According to Hofstra, *et al.* (2013) idiopathic MGN can be classified as an autoimmune illness because of recently found autoantibodies against an antigen on podocytes the M-type Phospholipase A2-receptor (PLA₂R1) that is present in 70% of patients with idiopathic MGN. Secondary causes of MGN include: drugs like NSAIDs, gold, and penicillamine; autoimmune illness like SLE and thyroiditis; infections like syphilis, hepatitis B

(HBV) and hepatitis C (HCV) as well as malignancies (especially solid tumours). Malignancies have been found in 19.4% of adults older than 60 years and in 4.1% of patients younger than 60 years (Hofstra & Wetzel, 2011).

On LM a homogeneous thickening of the glomerular capillary wall may be seen which later develop spikes and lucencies that is seen on silver methenamine staining. Ultra-structural examination is characterized by sub-epithelial electron dense deposits which correlates to immunoglobulin G (IgG) positive stained immune complexes on immunohistology (Couser & Cattran, 2010).

According to Sethi & Fervenza (2012) MPGN accounts for 7-10% of biopsy confirmed glomerulonephritis and is the third or fourth highest PGN causing ESRD. It has a variable clinical presentation ranging from asymptomatic protein and haematuria, acute nephritic syndrome or NS to rapidly progressive glomerulonephritis and CKD.

MPGN is a histopathological pattern of glomerular injury due to the deposition of immune complexes and/or complement factors in subendothelial, subepithelial and mesangial areas as a result of an underlying disease rather than being a specific diagnosis. The major clinical classification divides patients into disease due to autoimmune diseases like SLE and Rheumatoid Arthritis, infections – including viral (HCV and HBV), bacterial (endocarditis, visceral abscess etc.) and protozoal (malaria, schistosomiasis etc.) infections, cryoglobulinaemia, monoclonal gammopathy, neoplasia, chronic thrombotic microangiopathy and complement dysregulation or primary (idiopathic) MPGN if no specific aetiology is found.

On LM mesangial hypercellularity with endocapillary proliferation and capillary wall remodelling and duplication of the glomerular basement membrane with double contour formation and lobular accentuation of the glomerular tuft is seen.

Primary MPGN is traditionally subdivided according to the EM appearance and position of electron dense deposits and the kind of deposits including immunoglobulins, complement (complement factor 3 – C3) or a combination of the two as seen on IMF. MPGN 1 is the most common with subendothelial and mesangial deposits only. In MPGN 3 there are subepithelial and subendothelial deposits while MPGN 2 (Dense deposit disease - DDD) is characterized by dense immune complex deposition in the glomerular basement membrane and mesangium (Bomback & Appel, 2012; Fervenza, *et al.*, 2012, Sethi & Fervenza, 2012).

In MPGN1 deposits generally consists of immunoglobulins (IgG and/or immunoglobulin M) as well as complement components (C3 and/or complement factor 1). In MPGN 3 one variant (Burkholder variant) shows deposits with immunoglobulin and complement while another variant (Strife and Anders variant) shows C3 deposits alone or with immunoglobulins. However in MPGN 2 there is only C3 deposits. This has led to a proposed new classification for MPGN if immunoglobulins are present the term immunoglobulin-mediated MPGN will be used and C3 glomerulonephritis (DDD and C3 glomerulonephropathy) if only C3 deposits are present – these diseases have been found to be associated with dysregulation of the alternative complement pathway (Bomback & Appel; 2012).

MsPGN can have variable presentations including haematuria, proteinuria, hypertension and renal failure. It is characterized by a diffuse or focal proliferation of mesangial cells, an increase in the mesangial matrix with or without

complement or immunoglobulin deposits in the mesangium on biopsy. MsPGN is seen in immunoglobulin A nephropathy (IgAN) - the most frequent PGN in most countries, non-IgAN (seen predominantly in developing countries), immunoglobulin M nephropathy (IgM), SLE and the recovery phase of post-infectious glomerulonephritis (Vikse, *et al.*, 2002; Usha, *et al.*, 2008; Waikhom, *et al.*, 2012).

Important secondary glomerulonephritides include lupus nephritis, post infectious glomerulonephritis (PIGN) and diabetes.

SLE is a multisystem autoimmune illness in which 35% of patients have renal involvement at time of diagnosis and 50-60% of patients develop renal involvement within the first 10 years of the disease and of these 25% of patients will develop ESRD after 10 years of renal involvement (De Zubiria Salgado & Herrera-Diaz, 2012; Hahn, *et al.*, 2012).

Patients with lupus nephritis can have a wide range of presentations varying from asymptomatic urine abnormalities (AUA) to a rapid progressive glomerulonephritis (Bihl, *et al.*, 2006).

According to Hahn, *et al* (2012) patients are defined by the American College of Rheumatology (ACR) criteria as having renal involvement in the presence of one of the following:

1. persistent proteinuria of > 0.5 g /24h or a protein-creatinine ratio (PCR) > 0.5 or $> 3+$ protein on urine dipstick
2. Cellular casts

Lupus nephritis can be classified according to the current International Society of Nephrology / Renal Pathology Society (ISN/RPS) classification with prognostic and therapeutic implications as (Hahn, *et al.*, 2012, van Tellingen, *et al.*, 2012):

1. Class I: Minimal mesangial lupus nephritis - normal LM with minimal mesangial immune deposits on immunofluorescence.
2. Class II: Mesangioproliferative lupus nephritis - mesangial hypercellularity or matrix expansion on LM with mesangial immune deposits on Immunofluorescence.
3. Class III: Focal proliferative lupus nephritis - proliferative changes in <50% of glomeruli with subendothelial immune deposits on Immunofluorescence.
4. Class IV: Diffuse proliferative lupus nephritis - proliferative changes involving $\geq$ 50% of glomeruli with subendothelial immune deposits.
5. Class V: Membranous lupus nephritis - membranous thickening of glomerular capillaries with subepithelial immune deposits.
6. Class VI: Advanced sclerosing lupus nephritis with $\geq$ 90% globally sclerosed glomeruli.

PIGN is an immune mediated glomerulonephritis secondary to non-renal bacterial infection. Classically it has been described following latent group A streptococcal infection especially in children but in adults the infection may be present at the time of diagnosis (Infection related glomerulonephritis) and secondary to non-streptococcal infection – especially staphylococcal infection (Nasr, *et al.*, 2013). It has a high incidence in Africa and an associated poor

prognosis with 30-70% of adults developing CKD. (Naicker, *et al.*, 2007) Clinically patients present with features of nephritic syndrome, oedema, hypertension, haematuria, proteinuria and AKI. On LM the glomeruli are enlarged with hypercellularity due to proliferation of glomerular cells as well as infiltration by leucocytes. On immunofluorescence granular deposits of IgG and complement is seen along the glomerular basement membrane and mesangium. A characteristic feature seen on EM is subepithelial humps consisting of discrete amorphous electron dense deposits (Naicker, *et al.*, 2007).

DN is the leading cause of ESRD in most of the developed world (Zelmanovitz, *et al.*, 2009; Zocalli, *et al.*, 2010) and according to Keeton, *et al* (2004) a major cause of death in Type 2 diabetics in South Africa. The prevalence of DN in Sub-Saharan Africa is estimated around 6-16% (Naicker, 2013).

DN can be divided into 3 clinical stages: normo-albuminuria (<30mg/24h albuminuria), micro albuminuria (30-299mg/24h) and the macro albuminuric ($\geq$ 300mg/24h) stage associated with a decline in GFR (Zelmanovitz, *et al.*, 2009). On biopsy glomerular changes are seen with thickening of the glomerular basement membrane, mesangial expansion, nodular glomerulosclerosis (Kimmelstiel–Wilson lesion) and diffuse glomerulosclerosis in association with variable degrees of interstitial fibrosis and tubular atrophy (IFTA) and hyalinization of efferent and afferent arterioles (Zelmanovitz, *et al.*, 2009; Cohen Tervaert, *et al.*, 2010).

1.4.2 Tubulointerstitial diseases

TID include tubulointerstitial nephritis (acute or chronic), ATN, cortical necrosis, reflux nephropathy, oxalosis and nephrocalcinosis and myeloma cast nephropathy (Polito, *et al.*, 2010; Okpechi, *et al.*, 2011).

Acute tubulointerstitial nephritis (ATIN) most frequently presents as AKI while chronic tubulointerstitial nephritis presents with a more indolent course with features of tubular dysfunction like polyuria due to inability to concentrate urine or abnormal reabsorption of compounds resulting in e.g. phosphaturia, glycosuria and renal tubular acidosis (Beck, *et al.*, 2012).

Most primary TID are due to apoptosis and necrosis of the tubular epithelium caused by the chemical action of drugs and toxins that accumulate in the tubules or due to infection and inflammation of the tubulointerstitium (e.g. with chronic pyelonephritis or urinary reflux) or an increase in the intratubular pressure secondary to more distal obstruction. TID may also be idiopathic or due to an underlying genetic disease (López-Novoa, *et al.*, 2011).

1.4.3 Vascular diseases

Vascular diseases can be divided into hypertensive nephroangiosclerosis which include benign hypertensive nephroangiosclerosis (BHN) and malignant hypertensive nephroangiosclerosis (MHN), thrombotic microangiopathy (TMA), athero-embolic disease and pauci-immune crescentic glomerular nephropathy (small vessel vasculitides) (Mesquita, *et al.*, 2011; Okpechi, *et al.*, 2011).

The renovascular system can be involved as either micro or macrovascular diseases. The macrovascular diseases include acute arterial occlusion,

aneurysms and thrombosis of the renal artery or vein. These patients usually presents with abdominal pain, macroscopic haematuria and AKI.

Diseases that involve the microvasculature of the kidney invariably cause hypoperfusion of the kidney and alteration in renal function. Causes include TMA like malignant hypertension and thrombotic thrombocytopenic purpura as well as various vasculitides of the small vessels (López-Novoa, *et al.*, 2011; Textor & Leung, 2012).

1.5 Epidemiology of Renal Disease

1.5.1 Patterns of Renal Disease around the World

As pointed out by Sliem, *et al* (2011) long-term data collection and studies that include all known renal diseases are lacking but reports from various countries indicate variation in the incidence of renal disease according to the different population groups, demographics, environmental infective agents and socio-economic characteristics at different study sites.

Studies utilising various renal biopsy databases have reported that PGN seems to be present in about 50% of all native renal biopsies (Hanko, *et al.*, 2009).

A retrospective review of 9617 renal biopsy reports in Brazil found PGN to be the most frequent histopathological finding (51% of biopsies) followed by secondary glomerular disease (SGN) (22.6%), while TID accounted for only 2.2% of all biopsies (Polito, *et al.*, 2010).

In a comparison of categories of renal disease across Europe and Africa, PGN were the most frequent finding except for data from Cape Town and Belgium in

which SGN were the most frequent histopathological finding followed by PGN (Okpechi, *et al.*, 2012).

IgAN is the most frequent PGN in most of Asia, Western Europe, Australia and in white Americans while FSGS is the most common PGN in African Americans (Pesce & Schena, 2010). In Brazil the most common glomerulopathies are FSGS, MGN and IgAN (Polito, *et al.*, 2010) and in Saudi Arabia FSGS and MPGN are reported as the most frequent PGN (Ramprasad, 2000). Most studies from America, Europe, Asia, Australia and the Middle East found lupus nephritis to be the most common SGN (Pesce, *et al.*, 2009).

In an analysis of the native kidney biopsies included in the Spanish registry of glomerulonephritis from 1994 to 2009, Goicoechea, *et al* (2013) found the overall prevalence of ATIN to be 2.7% and for patients with AKI as indication for the biopsy, the prevalence increased to 13%. These authors also found an increase in the prevalence of ATIN during the last four years of their study especially in patients older than 65 years. According to Kodner and Kudrimoti (2003) ATIN accounts for up to 15% of admissions for AKI and is found in about 1% of biopsies performed for protein or haematuria. The most frequent causes of ATIN are drugs, infections and immune and neoplastic disorders (Kodner, *et al.*, 2003).

In a systematic review of studies from various countries on histopathology in septic AKI, Langenberg, *et al* (2008) report ATN to be present in only 22% of biopsies.

In a comparison of African and European data Okpechi, *et al* (2012) found that TID accounted for between 1.5% and 9.7% of all biopsy diagnoses while vascular diseases accounted for between 2.3% and 13.2%.

1.5.2 Patterns of Renal Disease in Africa

Published studies describing patterns of renal disease in Africa are quite scarce. In publications from sub-Saharan Africa both Senegal and Sudan report PGN to occur more frequently than SGN with FSGS as the most frequent PGN (Abdou, *et al.*, 2003; Khalifa, *et al.*, 2004).

A 10 year retrospective audit of referrals to the Renal Unit at the Universitas Academic Hospital in Bloemfontein South Africa from 1997-2006 found that the most common indication for biopsy was NS and on histology the most common PGNs were FSGS, MPGN, MGN and MCD (Jansen van Rensburg, *et al.*, 2010).

Data from Groote Schuur Hospital in Cape Town South Africa identified the most common PGNs as mesangiocapillary glomerulonephritis (MPGN¹) (20.4%), MsPGN (19.2%), MGN (18.5%), crescentic and necrotizing glomerulonephritis (11.4%) and FSGS (10.5%) and the most common secondary cause of glomerular disease was SLE. The most common indications for biopsy in this study were NS and AKI. Vascular diseases accounted for 18% of SGNs (Okpechi, *et al.*, 2011) and T1D for 9.7% of biopsies (Okpechi, *et al.*, 2012).

Seedat (1992) reported in a Kwazulu-Natal (KZN) based study that MPGN (47%) and MGN (25%) was the most frequent PGNs in black patients compared to MCD (18%) and MGN (18%) in Indian patients. When comparing the available data for sub-Saharan Africa with developed countries, studies show that

¹ Membranoproliferative glomerulonephritis and Mesangiocapillary glomerulonephritis are terms used to describe the same histopathological pattern of disease by various authors. When referring to either term it is used as used by the specific author but abbreviated as MPGN.

indications for renal biopsies are similar in most of Europe and Africa with the most common indication for biopsy being NS. In most European biopsy reports the most common PGN was IgAN but reports from Africa indicate that IgAN is rare and only accounts for 2.5% - 5.8% of PGNs (Okpechi, *et al.*, 2012).

1.5.3 Role of Age, Gender and Ethnicity

According to Cattran, *et al* (2003) MGN is the most frequent cause of adult onset NS followed by FSGS that is reported to be the cause of glomerulonephritis in 22% of adults and 33% of children. MCD accounts for 70-90% of NS in children and 10-15% of adults with patients older than 60 years accounting for a 25% of adults with MCD (Nachman, *et al.*, 2012).

Mohamed & John (2011) report that primary MGN and MCD as well as other renal diseases like pauci-immune glomerulonephritis (anti-neutrophil cytoplasmic antibodies (ANCA) – associated vasculitis), amyloidosis, myeloma cast nephropathy, athero-embolic renal disease and ATN occur more frequently in the elderly with the most frequent cause of NS in the elderly reported as MGN.

According to Silbiger & Neugarten (2008) the prevalence of FSGS, MGN and IgAN is slightly higher in adult males than in females – who also have slower progression to ESRD.

Lupus nephritis occurs more frequently in females (primarily in early adulthood) than in males in whom it has a worse prognosis (Ortega, *et al.*, 2010). The incidence of SLE in patients of black ethnicity is 2 to 5 times greater than in Caucasians and lupus nephritis occurs almost twice as frequently in black patients in whom it has a poorer prognosis (Korbet, *et al.*, 2007).

Contrary to IgAN that is generally accepted to be rare in patients of black ethnicity, FSGS has a higher incidence in African Americans than in Caucasians (Cattran, *et al.*, 2003). The collapsing and cellular variants of FSGS have a predilection for patients of African descent while the tip lesion, which has a better prognosis, occurs more frequently in white patients (Nachman, *et al* 2012).

The recent identification of the APOL1 G1 and G2 nephropathy risk variant gene in patients of African ancestry has been associated with a more rapid progression of non-diabetic renal disease to ESRD. In patients that are homozygous for APOL1 and who have untreated HIV infection 50% will develop HIVAN, and in the absence of HIV infection 18% of these patients develop FSGS (Freedman & Langefeld, 2012).

1.6 HIV and Renal Disease

HIV infection was first seen around 1930 in Africa and currently South Africa has the highest prevalence of HIV in the world (Swanepoel, *et al.*, 2012) with approximately 5.26 million South Africans being HIV positive (Statistics South Africa, 2013).

Kidney disease in patients with HIV was first recognized in 1984 in New York where a unique form of collapsing focal segmental glomerulonephritis (HIVAN) was described in a patient with acquired immunodeficiency syndrome (AIDS) and almost exclusively occurred in black patients. HIVAN was the leading cause of ESRD in African Americans but plateaued since the advent of antiretroviral therapy (Wyatt, *et al.*, 2009).

A systematic review of meta-analyses by Islam, *et al* (2012) found that the relative risk of renal disease was 3.87 times greater in HIV positive than HIV negative patients and that antiretroviral therapy (ARV) reduced the relative risk of renal disease by 46% when compared to patients that are ARV naïve.

Patients with HIV are at higher risk for the development of AKI and CKD. The most frequent causes of AKI in ambulatory HIV positive individuals are pre-renal azotaemia, ATN and drug related AKI (Estrella, *et al.*, 2010). Around 10-30% of HIV positive individuals have micro albuminuria or overt proteinuria with 2.4-10% of HIV positive individuals having a GFR < 60ml/min/1.73 m² (Estrella, *et al.*, 2010).

Risk factors for renal infection in HIV positive individuals include variants of the APOL1 gene, high viraemia, HCV co-infection. Traditional risk factors for renal disease like hypertension and diabetes are also increasing in HIV positive individuals on antiretrovirals with these two diseases now causing 50% of ESRD in HIV positive individuals in the USA (Estrella, *et al.*, 2010).

Lescure, *et al* (2012) reviewed the epidemiological data and histopathological patterns of glomerular disease in 88 HIV positive individuals that had glomerular disease on biopsies performed at Tenon University hospital in France between April 1995 and November 2007. In their biopsy group HIVAN was the most frequent glomerular disease (29.5%) followed by classical FSGS (26.1%) and immune-complex mediated glomerulonephritis (22.7%). Over the time period under investigation the frequency of HIVAN declined while classical FSGS increased statistically significantly.

A review of renal histologies in HIV positive patients at Groote Schuur Hospital in Cape Town from 2005 to December 2010 found the most common histopathological finding to be HIVAN (57.3%) – of these patients with HIVAN the 50% survival, in those who were not receiving ARV treatment, was 4.47 months (Wearne, *et al.*, 2012). Nearly 34.8% of patients in the study with features of HIVAN had an additional pathology on biopsy. The poor outcome in these patients emphasizes the need for early diagnosis of renal disease and ARV initiation in HIV positive patients.

In a two year retrospective review of 99 HIV positive and 48 HIV negative patients' renal biopsies from CHBAH in Gauteng, it was found that the top three glomerular diseases in HIV positive patients were HIVAN (27%), HIV immune complex kidney disease (21%) and MGN (13%) in comparison to the HIV negative patients the most common histopathological patterns were MGN (19%), FSGS (17%) and MCD (17%) (Gertholtz, *et al.*, 2006).

1.7 Aims and Objectives

From the literature it is clear that renal disease affects thousands of patients throughout the world at great human and financial cost. The literature review also brings to light that renal disease appears with different patterns of presentation and pathology in different areas of the world. In view of the paucity of data on the patterns of renal disease in Africans, and considering that from 2000 to 2004 the prevalence of ESRD in South Africa has increased by 54.5% (Bamgboye, 2006), the importance of additional data regarding the prevalence of various renal diseases in South Africa is clear. To address this need we undertook a

retrospective study of all native renal biopsies performed from 1 January 1982 to 31 December 2011 at the renal unit at CHBAH.

CHBAH serves a population of more than 3.6 million people in Soweto and its surrounding areas (Gauteng Department of Health and Social Development, 2011) and is one of the main referral centres for patients with renal disease. No recent long term data for the renal patient population of CHBAH has been published and as such we aimed to contribute to our knowledge regarding patterns of renal disease by:

1. Describing the histopathological patterns of renal disease at CHBAH
2. Identifying clinical pathological relationships between patient demographics, clinical presentations and histopathological diagnosis at CHBAH.
3. Comparing the patterns of renal disease between patients who are HIV positive and patients who are HIV negative at CHBAH.

2. METHODOLOGY

2.1 Study Design

This study consisted of a retrospective review of all renal histopathology reports from 1 January 1982 to 31 December 2011 for patients biopsied at CHBAH Renal unit.

2.2 Sample

All native renal biopsy reports at CHBAH, of male and female patients ages 12 years and above², on which the pathologist reviewing the specimen was able to make a definitive pathological diagnosis were included in the analysis. As such, exclusionary criteria for the study were biopsy reports on patients younger than 12 years of age, renal allograft biopsy reports and biopsy reports where the specimen was inadequate to derive a histopathological diagnosis.

2.3 Clinical and Laboratory Data Abstraction

Demographic data and histopathological diagnosis for each patient was collected from the available histopathology reports. All biopsy specimens were processed and reviewed by pathologists of the National Health Laboratory Service (NHLS) and prior to 2001 by the South African Institute of Medical Research. All specimens were processed by LM and IMF while EM was performed on some specimens. Laboratory results were obtained from the histological report if

² At CHBAH patients 12 years and older are viewed as adults in terms of nephrology treatment.

available; if results were unavailable the NHLS computerised results system was used to attempt to obtain outstanding data.

Data was recorded on a data collection sheet (see Appendix B) and then captured on a standard Microsoft Excel 2010 spreadsheet. Data recorded included the demographic profile (age, gender, ethnicity), haematological investigations, urine investigations, indication for biopsy and histopathological diagnosis for each patient.

2.3.1 Recording of Histological Diagnosis

Histopathological diagnosis was classified into 4 broad categories, adapted from Mesquita, *et al* (2011):

1. Primary glomerular diseases
2. Secondary glomerular diseases
3. Tubulointerstitial diseases
4. Miscellaneous / Other

Patients were considered to have a PGN if at the time of biopsy the patient had no report of a known systemic disease and had negative serology for HBV, HCV, HIV, syphilis, a negative anti-streptolysin O titre (ASOT), a negative anti-nuclear antibodies (ANA) and negative ANCA.

All patients with a glomerular disease that did not fulfil the criteria to be classified as a PGN were considered to have a SGN.

PGNs were divided into one of eight pathologies using an adapted classification method as used by Polito, *et al.*, (2010):

1. Minimal change disease
2. Membranous glomerulopathy
3. Focal segmental glomerulosclerosis
4. IgA nephropathy
5. Mesangioproliferative glomerulonephritis
6. Membranoproliferative glomerulonephritis
7. Crescentic glomerulonephritis
8. Proliferative glomerulonephritis

SGNs were subdivided according to the aetiological agent into 4 different categories adapted from Polito, *et al* (2010) and Okpechi, *et al* (2011):

1. Glomerulopathy secondary to a systemic disease (SD), including diseases such as lupus nephritis and other autoimmune disorders like Rheumatoid arthritis and mixed connective tissue disorder.
2. Glomerulopathy secondary to infectious diseases (ID), including HIV, HBV, HCV, syphilis, PIGN and others.
3. Glomerulopathy associated with a metabolic disease or deposits (MD), including DN, amyloidosis, light chain deposition disease, glomerular diseases with patterned or organized deposits – immunotactoid GN and fibrillary GN.

4. Glomerulopathy secondary to vascular diseases (VD), including BHN and MHN, TMA, pre-eclampsia or the haemolysis elevated liver enzymes low platelet syndrome (HELLP), athero-embolic renal disease, systemic sclerosis and pauci-immune crescentic glomerulonephritis.

Diseases classified as TID include: interstitial nephritis (IN), ATN, pyelonephritis and interstitial renal disease secondary to myeloma.

Miscellaneous diseases included unclassified diseases: end stage kidney of unknown aetiology and unclassified glomerulonephritis, hereditary diseases (HR) including Alport's nephritis, thin basement membrane disease, oxalate nephropathy and Fabry's disease, tumours (TU) and normal histology.

2.3.2 Recording of Clinical Presentation / Indication for Biopsy

Clinical indications obtained from pathology reports were subdivided as:

1. AKI
2. AUA
3. CKD
4. Haematuria
5. Hypertension
6. NS
7. Nephritic syndrome
8. Nephritic nephrotic syndrome
9. Unknown

2.4 Data Analysis

Data was entered into a Microsoft Excel 2010 spreadsheet and then transferred to SPSS 20 statistical software package for statistical analysis. Descriptive statistics consisting of means and standard deviation were calculated for patient age. Frequency distributions of further demographic data (sex, ethnicity), clinical presentations and histopathological diagnosis were calculated and expressed as proportions. Cross tabulations between the variables of interest were performed. As the data for the variables of interest in the study were nominal/categorical level data the chi-square test of independence was used to evaluate the potential statistical significance of apparent associations between variables (Plichta & Kelvin, 2013). Where a chi-square value was calculated, a p-value of < 0.05 was considered significant.

To identify potential changes in renal disease patterns over a meaningful time frame and to allow comparison with data from similar studies, the 30 year period for which biopsy results were available, was divided into three 10 year periods, namely: 1 January 1982 to 31 December 1991, 1 January 1992 to 31 December 2001 and 1 January 2002 to 31 December 2011.

2.5 Ethics

This study was approved by the Human Research ethics committee (Medical) of the University of the Witwatersrand Clearance Certificate number: M120874 (see Appendix A). This study did not require informed consent from patients as the study made use of existing histology reports where no interaction with patients occurred and all identifying information (patients names and hospital numbers) were removed from the data set.

3. RESULTS

3.1 Overview of Records Reviewed

A total of 1848 histopathology reports were reviewed for patients at CHBAH who had a native renal biopsy between 1 January 1982 and 31 December 2011 that was adequate to make a histopathological diagnosis. Between 1 January 1982 to 31 December 1991 a total of 570 biopsies were performed, during the 10 year period from 1 January 1992 to 31 December 2001 a total of 377 biopsies were performed and 901 biopsies were performed between 1 January 2002 to 31 December 2011.

3.2 Demographic Analysis

The major demographic characteristics of the study sample, broken down into the three 10 year periods, as well as for the overall study period, are summarized in Table 3.1.

The mean age of all patients biopsied was 33.5 ± 12.6 years. The youngest patient biopsied was 12 years old and the oldest patient 78 years. A total of 35 patients had no age recorded and only reported as adult female / male (Table 3.1).

There was a slightly higher number of females in the study sample at 50.2% (928 patients) while males accounted for 49.8% (920 patients).

The majority of patients were black (96.4%, 1782 patients) – the frequencies of other ethnicities were relatively small with 1.6% coloured patients (29 patients), 1.4% white (26 patients) and 0.6% Indian (11 patients).

Table 3.1 Demographic data

	01/01/1982 - 31/12/1991	01/01/1992 - 31/12/2001	01/01/2002 - 31/12/2011	01/01/1982 - 31/12/2011
Female	49.1% (n=280)	54.6% (n=206)	49.1% (n=442)	50.2% (n=928)
Male	50.9% (n=290)	45.4% (n=171)	50.9% (n=459)	49.8% (n=920)
Mean age	32.3 ± 12.9 years	30.6 ± 11.3 years	35.3 ± 12.6 years	33.5 ± 12.6
<20 years old	17.5% (n=100)	17% (n=64)	9.5% (n=86)	13.5 % (n=250)
20-39 years	52.6% (n=300)	58.9% (n=222)	54.7% (n=493)	54.9% (n=1015)
40-59 years	25.6% (n=146)	18.3% (n=69)	30.4% (n=274)	26.5% (n=489)
≥ 60 years	3.5% (n=20)	0.8% (n=3)	4.0% (n=36)	3.2% (n=59)
Missing ages	0.7% (n=4)	5.0% (n=19)	1.3% (n=12)	1.9% (n=35)
Black	99.3% (n=566)	96.6% (n=364)	94.6% (n=852)	96.4% (n=1782)
Coloured	0.4% (n=2)	1.9% (n=7)	2.2% (n=20)	1.6% (n=29)
White	0.2% (n=1)	0.8% (n=3)	2.4% (n=22)	1.4% (n=26)
Indian	0.2% (n=1)	0.8% (n=3)	0.8% (n=7)	0.6% (n=11)

3.3 Indications for Renal Biopsy

The indications for biopsy and the change in their prevalence over time are summarized in Table 3.2. Around 47.7% of all patients had biopsies performed for NS / nephrotic range proteinuria, 19.8% for AKI and 8.1% for AUA.

Table 3.2 Indications for renal biopsies

	01/01/1982- 31/12/1991	01/01/1992- 31/12/2001	01/01/2002- 31/12/2011	01/01/1982- 31/12/2011	p-values
AKI	12.3% (n=70)	15.4% (n=58)	26.4% (n=238)	19.8% (n=366)	p<0.001
AUA	3.9% (n=22)	10.1% (n=38)	10.0% (n=90)	8.1% (n=150)	p<0.001
CKD	7.0% (n=40)	2.1% (n=8)	7.9% (n=71)	6.4% (n=119)	p=0.001
H	2.6% (n=15)	1.1% (n=4)	1.3% (n=12)	1.7% (n=31)	p=0.085
HT	12.5% (n=71)	3.4% (n=13)	4.3% (n=39)	6.7% (n=123)	p<0.001
N	0.4% (n=2)	1.3% (n=5)	0.6% (n=5)	0.6% (n=12)	*
NN	6.0% (n=34)	8.2% (n=31)	5.4% (n=49)	6.2% (n=114)	p=0.114
NS	51.1% (n=291)	53.3% (n=201)	43.2% (n=389)	47.7% (n=881)	p<0.001
Unknown	4.4% (n=25)	5.0% (n=19)	0.9% (n=8)	2.8% (n=52)	*

AKI (Acute kidney injury); AUA (Asymptomatic urine abnormalities); CKD (Chronic kidney disease); H (Haematuria); HT (Hypertension); N (Nephritic syndrome); NN (Nephritic nephrotic syndrome); NS (Nephrotic syndrome).

* Due to the small number represented in the sample, a Chi square and associated p-value could not be calculated.

3.3.1 Indications for Biopsy and Associated Histological Findings

The most frequent histological findings in patients biopsied for NS over the whole study period were FSGS (19.8%), MGN (19.2%), lupus nephritis (12.3%), MCD (11.0%), MPGN (10.6%) and HIVAN (4.4%). However the proportions of the histopathological findings varied over the three 10 year periods. Between 1982 and 1991 MGN (21.6%), FSGS (19.9%) and MCD (16.5%) were the most frequent findings, while MGN (19.4%), lupus nephritis (19.4%) and FSGS (18.9%) were the most frequent findings between 1992 and 2001. Between 2002 and 2011 FSGS (20.1%) followed by MGN (17.2%) and lupus nephritis (12.9%) were the most frequent findings in patients biopsied for NS.

The frequencies of findings in patients biopsied for NS differed according to age. In patients younger than 20 years biopsied for NS the most frequent findings were FSGS (29.1%), MGN (17.6%), MCD (15.2%) and MPGN (15.2%), for patients 20-39 years of age MGN (18.9%), FSGS (18.5%), lupus nephritis (15.3%) for patients aged 40-59 years old, MGN (19.5%), FSGS (14.1%), MPGN (10.8%) and patients 60 years and older, MGN (41.2%), FSGS (17.6%), BHN (17.6%).

Of patients biopsied for AKI 16.9% had HIVAN, 15.0% ATN, 9.0% lupus nephritis, 8.5% MHN, 8.5% IN and 8.2% FSGS while the most frequent findings in patients biopsied for AUA were lupus nephritis (80.0%), human immunodeficiency virus immune complex disease (HIV-ICD) (4.0%), normal kidney (3.3%), IN (2.0%) and FSGS (2.0%).

3.3.2 Indications for Biopsy over Time

When looking at the association between indications for biopsy over time, the proportion of AKI increased ($p<0.001$), an increase in the proportion of AUA ($P<0.001$) was noted after the first 10 year period (1982-1991) as well as a significant increase ($p=0.001$) in the proportion of biopsies performed for CKD from the second 10 year period (1992-2001) to the third 10 year period (2002-2011). The proportion of biopsies performed for HT decreased after the first 10 year period ($p<0.001$) and the proportion of NS decreased from the second to third 10 year period ($p<0.001$).

3.3.3 Indications for Biopsy Associated with Gender, Ethnicity and Age

Gender differences in biopsy indications were found with 13.9 % ($n=126$) of females biopsied for AUA compared to 2.7% ($n=24$) of males ($p<0.001$). Around 8.3% ($n=74$) of males and 5.0% ($n=45$) of females were biopsied for CKD ($p=0.005$) while 8.1% ($n=72$) of males and 4.6% ($n=42$) of females were biopsied for nephritic nephrotic syndrome (NN) ($p=0.003$).

NS was the most frequent indication for biopsy across all ethnicities - black (49.0%), coloured (51.7%), whites (50.0%) and Indian (40.0%).

Age differences in indications for biopsy were found for AKI and NS. AKI as indication for biopsy increased with age accounting for 8.6% in patients < 20years, 19.9% in 20-39 year olds, 24.8% in 40-59 year olds and 37.9% in patients of 60 years and older ($p<0.001$) while NS decreased with age accounting for 67.6%, 50.4%, 39.2% and 29.3% for the same four ascending age groups ($p<0.001$).

3.4 Histological Findings

The most frequent findings on histological examination of specimens were PGN at 39.7% followed by histopathological changes secondary to ID at 16.2% and changes secondary to SD at 15.3%. A total of 17 biopsy specimens (0.9%) were found to have no abnormality on histological examination.

Overall, the combined SGNs - which included ID, MD, SD, and VD – occurred more frequently than PGN and were found in a total of 911 biopsies (49.3%).

HR was found in only 5 patients (0.3%), 2 patients (0.1%) had Alport's disease, 1 patient (0.05%) had thin basement membrane disease, 1 (0.05%) Oxalate nephropathy (primary hyperoxalosis) and 1 patient (0.05%) had Fabry's disease.

3.4.1 Histological Findings over Time

Significant changes in frequencies over time were noted for PGNs which decreased over time ($p < 0.001$), accounting for 48.1% ($n=274$) of biopsies between 1982 and 1991, 44.3% ($n=167$) of biopsies performed between 1992 and 2001 and 32.5% ($n=293$) of biopsies between 2002 and 2011.

SGN increased over time and accounted for 37.7% ($n= 215$) of biopsies between 1982 and 1991, 47.5% ($n=179$) of biopsies from 1992 to 2001 and 57.4% ($n=517$) of biopsies from 2002 to 2011 ($p < 0.001$).

Of the SGNs the proportion of ID increased significantly over time ($p < 0.001$) and VD decreased significantly from the first to second 10 year period ($p=0.001$) while the proportion of SD increased significantly for the same period ($p < 0.001$).

3.4.2 Histological Findings and Gender

Gender differences in frequencies of nephropathies were found with statistically significant more males (45.3% vs. 34.2%; $p<0.001$) than females who had PGNs, VD (14.7% vs. 11.0%; $p=0.018$), TID (9.2% vs. 5.5%; $p=0.002$) and biopsies in the unclassified group (3.4% vs. 1.4%; $p=0.006$) while more females had SGNs (57.5% vs. 41.0%; $p<0.001$) and SD (27.2% vs. 3.3%; $p<0.001$).

3.4.3 Histological Findings and Ethnicity

Looking at ethnicity and PGN, 702 black patients (39.6%), 7 coloured (24.1%), 5 Indian (45.5%) and 16 white (61.5%) patients had PGN.

SGN was the most frequent finding in black (49.2%) and coloured (75.9%) patients; in Indian patients SGN and PGN occurred at the same frequency (45.5%) while in white patients PGN were the most frequent finding at 61.5%. There was no statistically significant association between ethnicity and the major histological groups or any pathologies.

3.4.4 Histological Findings and Age

PGN occurred at a higher frequency in patients younger than 20 years than other age groups while SGN occurred less frequently in the patients younger than 20 years ($p<0.001$). SD occurred more frequently in young adults between 20-39 years than patients of 40 years and older ($p<0.001$). VD occurred more frequently in patients between 40-59 years of age than in patients younger than 20 years ($p<0.001$). TID frequency increased with increase in age ($p<0.001$).

The proportions of histological findings with p-values for the association of nephropathies and the time periods are summarized in Table 3.3.

Table 3.3 Proportions of nephropathies

	01/01/1982- 31/12/1991	01/01/1992- 31/12/2001	01/01/2002- 31/12/2011	01/01/1982- 31/12/2011	p-values
HR	0.2% (n=1)	0.3% (n=1)	0.3% (n=3)	0.3% (n=5)	*
ID	8.8% (n=50)	11.4% (n=43)	22.9% (n=206)	16.2% (n=299)	p<0.001
MD	4.6% (n=26)	5.3% (n=20)	5.2% (n=47)	5.0% (n=93)	p=0.824
Normal	0.9% (n=5)	1.9% (n=7)	0.6% (n=5)	0.9 % (n=17)	*
PGN	48.1% (n=274)	44.3% (n=167)	32.5% (n=293)	39.7% (n=734)	p<0.001
SD	8.1% (n=46)	23.1% (n=87)	16.5% (n=149)	15.3% (n=282)	p<0.001
TID	7.2% (n=41)	5.3% (n=20)	8.3% (n=75)	7.4% (n=136)	p=0.166
TU	0.1% (n=1)	0.0% (n=0)	0.0% (n=0)	0.1% (n=1)	*
VD	16.3% (n=93)	7.7% (n=29)	12.8% (n=115)	12.8% (n=237)	p=0.001
Unclassified	5.8% (n=33)	0.8% (n=3)	0.9% (n=8)	2.4% (n=44)	P<0.001

HR (Inherited diseases); ID (Infectious diseases); MD (Metabolic and deposit diseases); PGN (Primary glomerular diseases); SD (Systemic diseases); TID (Tubulointerstitial diseases); TU (Tumours); VD (Vascular diseases).

* Due to the small number represented in the sample, a Chi square and associated p-value could not be calculated.

3.5 Primary and Secondary Glomerular Diseases

Of the different types of PGNs and SGNs, the most frequent PGN during the 30 year period was FSGS (29.6%) followed by MGN (25.7%), MPGN (18.1%), MCD (14.3%) and MsPGN (6.5%). IgAN accounted for only 3.5% of all PGNs. ID was the most frequent cause of SGN accounting for 32.8%, followed by SD at 31.0%, VD at 26.0% and MD 10.2%. DN accounted for only 6.6% of SGN and was present in 3.2% (n=60) of all biopsies, only 50 patients were known to be diabetic at the time of biopsy and 16 of the patients with DN were known to be HIV positive.

The most frequent clinical indications for biopsy in patients with PGNs were NS (74.9%), NN (8.3%) and AKI (7.7%) and when looking at IgAN specifically most

patients were biopsied for NS (23.1%), AKI (15.4%), CKD (11.5%), Haematuria (11.5%) and NN (11.5%), while for SGNs the most frequent indications were NS (36.0%), AKI (22.9%) and AUA (14.9%).

3.5.1 Time

The proportions of the most frequent PGNs across the three different 10 year periods changed with FSGS (25.2%), MGN (24.5%) and MCD (19.3%) occurring most frequently in the first 10 year period. During the second 10 year period MGN (29.9%) was the most frequent followed by FSGS (24.0%) and MPGN (24%). During the third 10 year period FSGS (36.9%), MGN (24.6%) and MPGN (17.4%) were the most frequent. The decrease in frequency of MCD from the first to second 10 year period was statistically significant ($p=0.006$), as was the increase of FSGS from the second to third 10 year period ($p=0.002$) with a concurrent decrease in MPGN during the same time period ($p=0.068$).

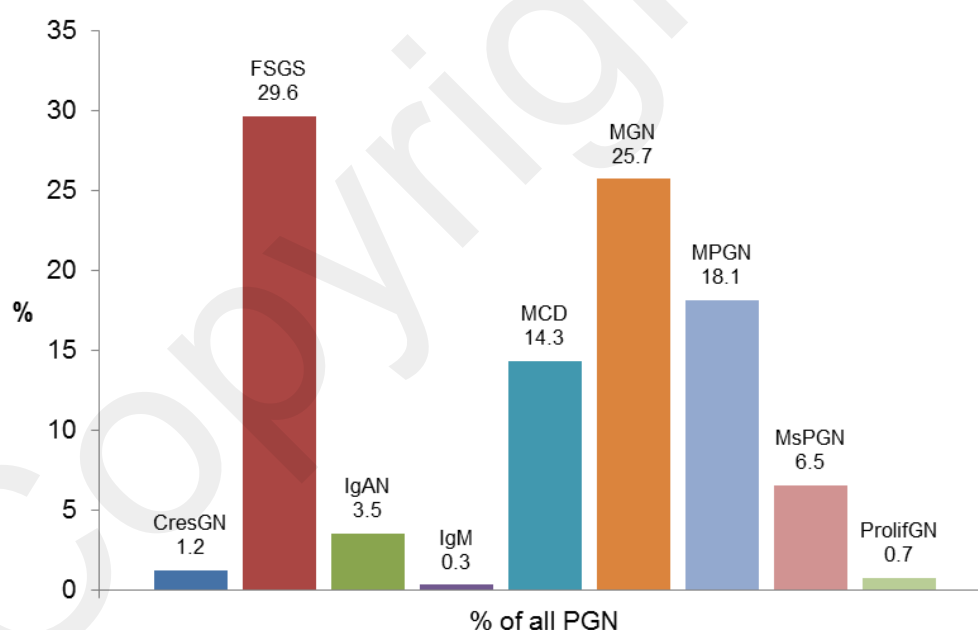
The proportions of the different PGNs during the different 10 year periods are summarized in Table 3.4 and the overall proportions for the period 1982-2011 are illustrated in Figure 3.1. The contributors to SGN are summarized in Table 3.5. Table 3.6 and Figure 3.2 provide a summary of the different SGNs over the different 10 year periods as well as their overall contributions to SGN for the entire study period. Pertinent details of the different SGNs are highlighted in the sections to follow.

Table 3.4 Proportions of PGNs over the different 10 year periods

	01/01/1982- 31/12/1991	01/01/1992- 31/12/2001	01/01/2002- 31/12/2011	p-values
CresGN	1.5% (n=4)	1.8% (n=3)	0.7% (n=2)	*
FSGS	25.2% (n=69)	24.0% (n=40)	36.9% (n=108)	p=0.002
IgAN	4.4% (n=12)	3.0% (n=5)	3.1% (n=9)	p=0.638
IgM	0.4% (n=1)	0.6% (n=1)	0.0% (n=0)	*
MCD	19.3% (n=53)	9.0% (n=15)	12.6% (n=37)	p=0.006
MGN	24.5% (n=67)	29.9% (n=50)	24.6% (n=72)	p=0.370
MPGN	15.3% (n=42)	24.0% (n=40)	17.4% (n=51)	p=0.068
MsPGN	7.7% (n=21)	7.8% (n=13)	4.8% (n=14)	p=0.290
ProlifGN	1.8% (n=5)	0.0% (n=0)	0.0% (n=0)	*

CresGN (Crescentic glomerulonephritis); FSGS (Focal segmental glomerulosclerosis); IgAN (Immunoglobulin A nephropathy); IgM (Immunoglobulin M nephropathy); MCD (Minimal change disease); MGN (Membranous glomerulopathy / glomerulonephritis); MPGN (Membranoproliferative glomerulonephritis); MsPGN (Mesangioproliferative glomerulonephritis); ProlifGN (Proliferative glomerulonephritis).

* Due to the small number represented in the sample, a Chi square and associated p-value could not be calculated.



CresGN (Crescentic glomerulonephritis); FSGS (Focal segmental glomerulosclerosis); IgAN (Immunoglobulin A nephropathy); IgM (Immunoglobulin M nephropathy); MCD (Minimal change disease); MGN (Membranous glomerulopathy / glomerulonephritis); MPGN (Membranoproliferative glomerulonephritis); MsPGN (Mesangioproliferative glomerulonephritis); ProlifGN (Proliferative glomerulonephritis).

Figure 3.1 PGN proportions from 1 January 1982 to 31 December 2011

Table 3.5 Proportions of SGN groups

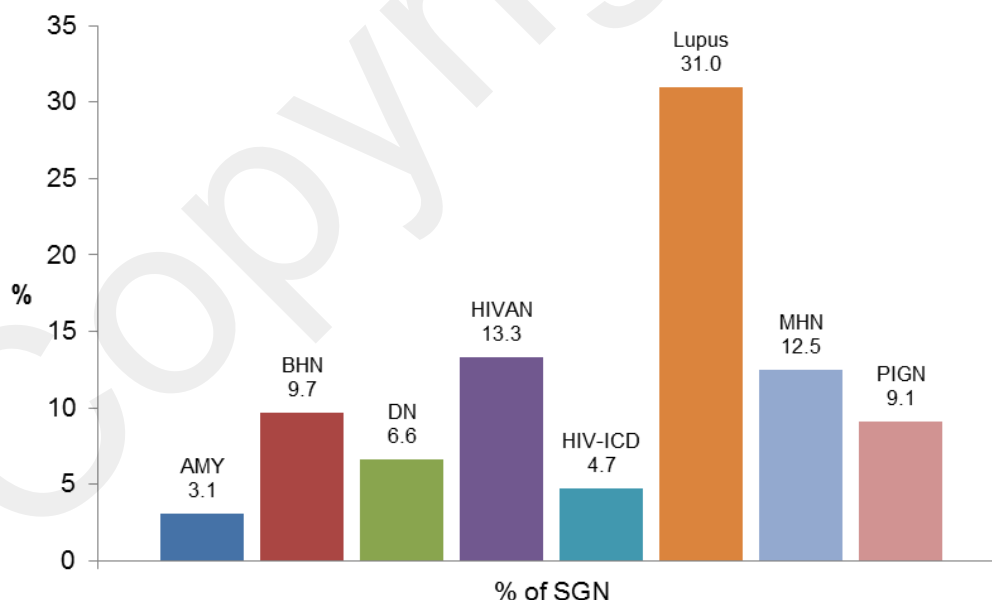
	01/01/1982- 31/12/1991	01/01/1992- 31/12/2001	01/01/2002- 31/12/2011	01/01/1982- 31/12/2011
ID	5.5% (n=50)	4.7% (n=43)	22.6% (n=206)	32.8% (n=299)
MD	2.9% (n=26)	2.2% (n=20)	5.2% (n=47)	10.2% (n=93)
SD	5.0% (n=46)	9.5% (n=87)	16.4% (n=149)	31.0% (n=282)
VD	10.2% (n=93)	3.2% (n=29)	12.6% (n=115)	26.0% (n=237)

ID (Infectious diseases); MD (Metabolic and deposit diseases); SD (Systemic diseases); VD (Vascular diseases).

Table 3.6 Most frequent SGNs for each 10 year period

	01/01/1982- 31/12/1991	01/01/1992- 31/12/2001	01/01/2002- 31/12/2011	p-values
AMY	7.4% (n=16)	2.2% (n=4)	1.5% (n=8)	p<0.001
BHN	22.3% (n=48)	2.2% (n=4)	7.0% (n=36)	p<0.001
DN	4.7% (n=10)	8.9% (n=16)	6.6% (n=34)	p=0.232
HIVAN	0.5% (n=1)	6.7% (n=12)	20.9% (n=108)	p<0.001
HIV-ICD	0.0% (n=0)	0.0% (n=0)	8.3% (n=43)	p<0.001
Lupus	21.4% (n=46)	48.6% (n=87)	28.8% (n=149)	p<0.001
MHN	19.1% (n=41)	7.3% (n=13)	11.6% (n=60)	p=0.001
PIGN	16.7% (n=36)	13.4% (n=24)	4.4% (n=23)	p<0.001

AMY (Amyloidosis); BHN (Benign hypertensive nephroangiosclerosis); DN (Diabetic Nephropathy); HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); Lupus (Lupus Nephritis); MHN (Malignant hypertensive nephroangiosclerosis); PIGN (Post infectious glomerulonephritis).



AMY (Amyloidosis); BHN (Benign hypertensive nephroangiosclerosis); DN (Diabetic Nephropathy); HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); Lupus (Lupus Nephritis); MHN (Malignant hypertensive nephroangiosclerosis); PIGN (Post infectious glomerulonephritis).

Figure 3.2 The most frequent SGNs over 30 years

3.5.2 Gender

The most common PGN in females and males was FSGS accounting for 33.4% (n=106) and 26.6% (n=111) respectively with primary FSGS occurring slightly more frequently in females than males (p=0.045). The second most frequent PGN in both genders was MGN (27.4%, n= 87 and 24.5%, n=102; p=0.360). MPGN was the third most frequent PGN in males, more males than females had primary MPGN (p<0.001) where MPGN, accounted for 10.7% (n=34) of PGN in females and 23.7% (n=99) in males. The third most frequent PGN in females was MCD accounting for 16.1% (n= 51) of PGN in females and 12.9% (n=54) in males (p=0.229).

When looking at associations of SGNs and gender, only lupus nephritis occurred more frequently in females than in males (47.2%, n=252 vs. 8.0%, n=30; p <0.001) while a greater proportion of males than females had the following pathologies: BHN (14.6%, n=55 vs. 6.2%, n=33; p<0.001), MHN (16.4%, n=62 vs. 9.7%, n=52; p=0.003), DN (9.3%, n=35 vs. 4.7%, n=25; p=0.006) secondary MGN (2.9%, n=11 vs. 0.9%, n=5; p=0.025) and PIGN (12.5%, n=47 vs. 6.7%, n=36; p=0.003).

3.5.3 Age and Ethnicity

In patients younger than 20 years old the three most frequent PGNs were FSGS (35.2%), MPGN (20.8%) and MGN (18.9%), for 20-39 year olds FSGS (26.1%), MGN (26.1%) and MPGN (17.6%), for 40-59 year olds FSGS (30.3%), MGN (29.6%) and MPGN (19.0%), and for patients aged 60 and older the two most frequent PGN were FSGS (40.0%) and MGN (40.0%). The majority of

patients with IgAN were between 20-39 years (76.9%, n=20, p=0.126). No statistically significant associations between PGN and the different age groups were found.

The proportions of the PGNs for the different ethnic groups are shown in Figure 3.3 and the most frequent findings in the different ethnic groups are shown in Table 3.7. Lupus nephritis was the most frequent SGN in this study for all ethnicities except for white patients in whom MHN (37.5% n=3) occurred at a higher frequency than lupus nephritis (25% n=2).

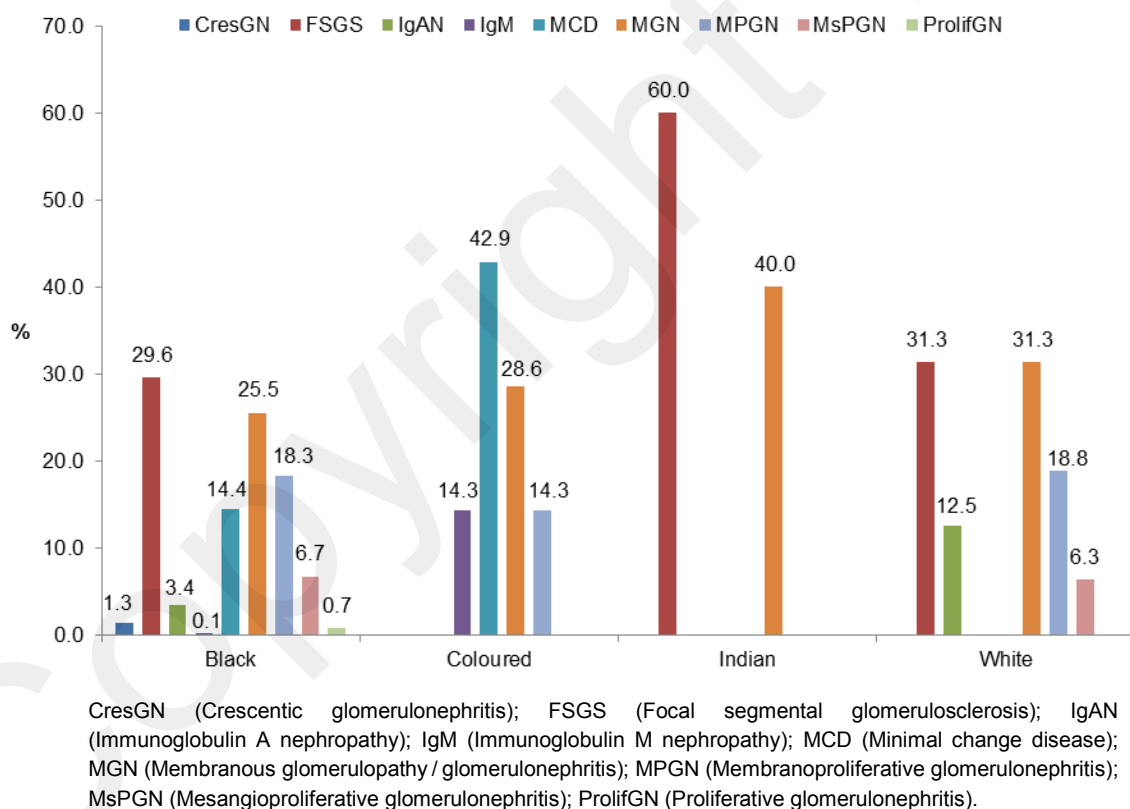


Figure 3.3 Proportions of PGNs for the different ethnicities

Table 3.7 Most frequent renal diseases for the different ethnic groups

Race	Findings		
Black	Lupus Nephritis (15.1%, n=269)	FSGS (12.4%, n=221)	MGN (11.0%, n=196)
Coloured	Lupus Nephritis (27.6%, n=8)	MHN (17.2%, n=5)	PIGN & MCD (10.3%, n=3)
Indian	Lupus Nephritis (27.3%, n=3)	FSGS (27.3%, n=3)	MGN (18.2%, n=2)
White	FSGS (19.2%, n=5)	MGN (19.2%, n=5)	MPGN & MHN (11.5%, n=3)

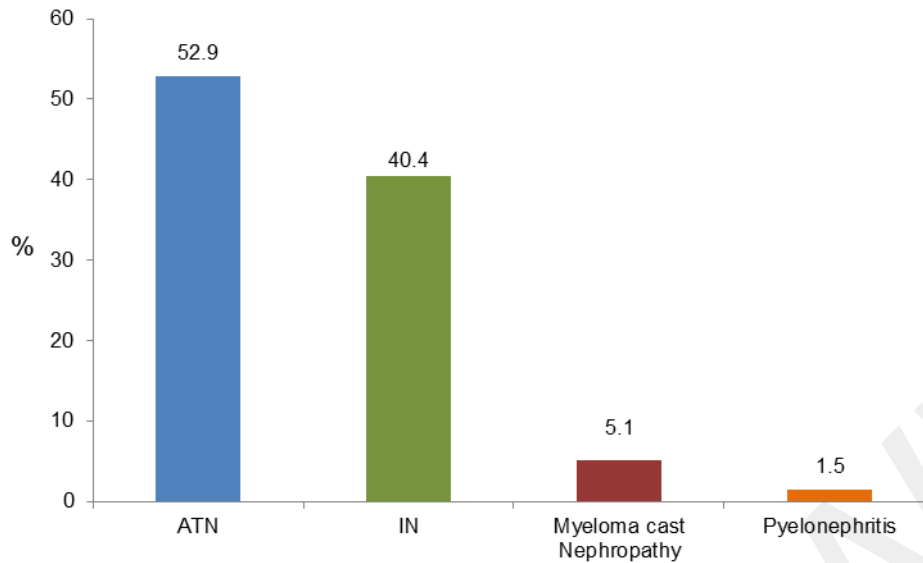
FSGS (Focal segmental glomerulosclerosis); MGN (Membranous glomerulopathy / glomerulonephritis); MHN (Malignant hypertensive nephroangiosclerosis); MPGN (Membranoproliferative glomerulonephritis); PIGN (Post infectious glomerulonephritis).

3.6 Tubulointerstitial Diseases

TID were found in 7.4% (n=136) of all biopsies during the study period. In most patients with TID the biopsy was performed for AKI (68.4%) or CKD (11.0%).

The most frequent TID were ATN (52.9%, n=72) followed by IN (40.4%, n=55) with myeloma cast nephropathy and pyelonephritis accounting for only 5.1% and 1.5% respectively.

There was no statistically significant association between the year periods and TID ($p=0.166$). Myeloma cast nephropathy was exclusively diagnosed between 2002-2011. More males than females had ATN (5.3%, n=49 and 2.5%, n=23 of all biopsies; $p=0.002$). TID occurred exclusively in patients of black ethnicity. Most patients with TID were between 20-39 years (46.3%) and 40-59 years (35.3%) old and although TID constituted 28.8% of all nephropathies in patients 60 years and older no statistically significant age group associations were found for TID and its contributors. The proportions of the various TID are shown in Figure 3.4.



ATN (Acute tubular necrosis); IN (Interstitial nephritis).

Figure 3.4 Proportions of TID from 1 January 1982 to 31 December 2011

3.7 Vascular Diseases

A total of 237 (12.8%) of biopsies had VD. The most frequent VD were MHN (48.1%, n=114), BHN (37.1%, n=88) and TMA (6.3%, n=15). During the 30 year period 5 patients (0.3%) had pauci-immune FSGN and 2 patients (0.1%) granulomatosis with polyangiitis / Wegener's granulomatosis (GPA) and 11 patients (0.6%) had features of vasculitis on biopsy.

Hypertension (38.0%, n=90) was the most frequent indication for biopsy in patients with VD followed by AKI (30.0%, n=71) and CKD (14.8%, n=35).

Changes over time were noted for BHN and MHN ($p < 0.001$ and $p = 0.044$ respectively) which both decreased from the first 10 year period (1982-1991) to the second 10 year period (1992-2002).

Of VD only BHN occurred statistically significantly more frequently in males (62.5%, n=55) than females (37.5% n= 33) had BHN ($p = 0.014$).

Most of the patients where VD were diagnosed were between 20-39 years (50.2%, n=119) and 40-59 years (42.2%, n=100). Most patients with MHN were young adults between 20-39 years old (57.9%, n=66) while BHN were most frequently found in patients between 40-59 years old (53.4%, n= 47).

The different proportions of diseases categorized as VD are shown in Figure 3.5.

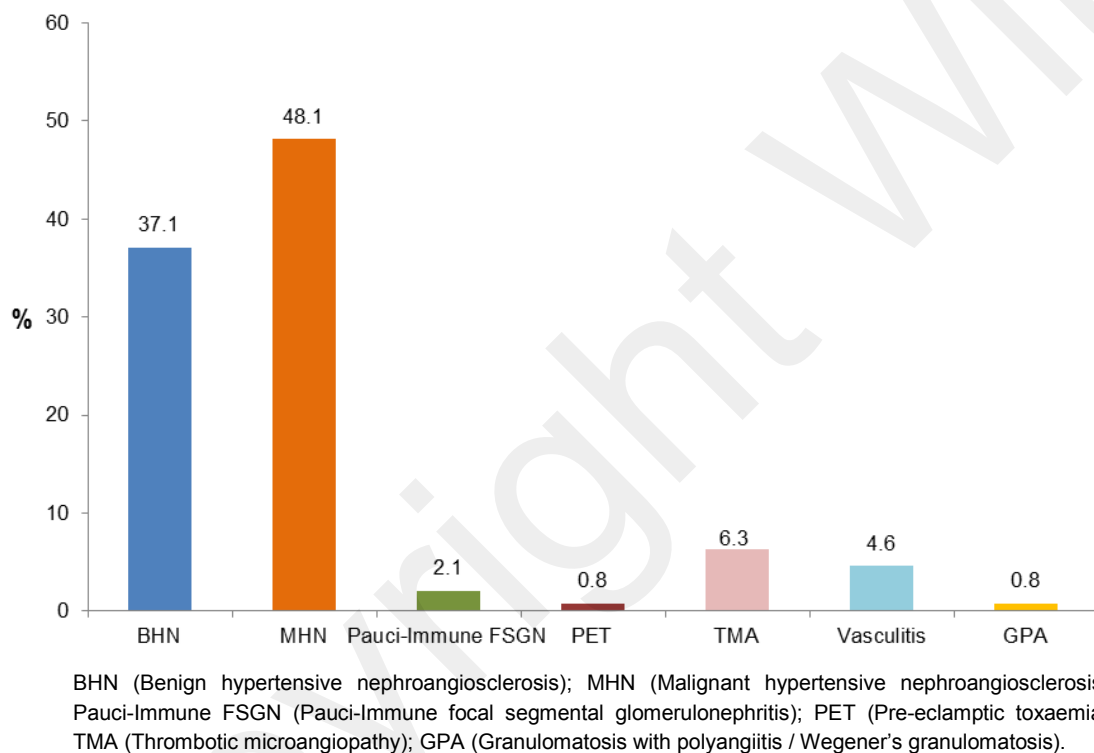


Figure 3.5 Proportions of VD from 1 January 1982 to 31 December 2011

3.8 Metabolic Diseases

Metabolic associated glomerular diseases were diagnosed in 93 patients (5.0%).

The most frequent indications for biopsy in patients with MD were NS (62.4%, n=58), CKD (17.2%, n=16) and AKI (14.0%, n=13).

No significant change occurred in MD over time, however amyloidosis (AMY) as diagnosis decreased over time ($p=0.010$) while DN increased from 1.8% of all biopsies between 1982 and 1991 to 4.2% between 1992 and 2001 ($p=0.049$).

There were no significant gender frequency differences in the most frequent MDs. The gender distribution for AMY was 15 females (53.6%) and 13 males (46.4%) ($p=0.721$) while 25 females (41.7%) and 35 males (58.3%) had DN ($p=0.178$). The different proportions of diseases categorized as MD are shown in Figure 3.6.

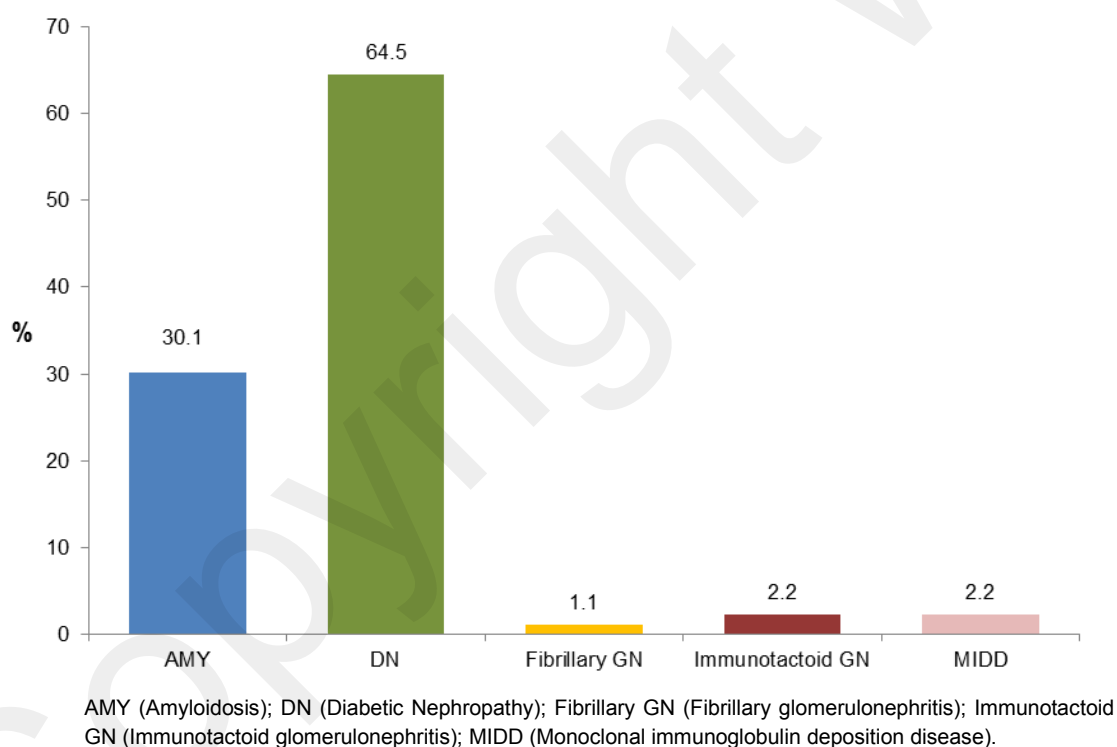


Figure 3.6 Proportions of MD from 1 January 1982 to 31 December 2011

3.9 Virological Infections

A total of 1267 patients (68.6%) had documented results available for HIV, 704 patients (38.1%) for HBV and 540 patients (29.2%) for HCV for the period under review (see Table 3.8).

The proportion of patients with a confirmed HIV result increased steadily over the study period. From 1982 to 1991, 23.2% of patients had a confirmed HIV result, this increased to 73.7% during the second ten year period (1992-2001) and 95.1% for the last ten year period between 2002 to 2011.

Of all patients biopsied over the entire study period, 19.7% were documented to be HIV positive. Looking at only confirmed HIV results, the proportion of patients with a positive HIV result increased significantly during the study period; 0.8% of patients had a HIV positive result between 1982 to 1991, 7.9% between 1992-2001 and 39.8% between 2002-2011 ($p < 0.001$). The proportion of patients documented to be HIV positive between 1 January 2002 and 31 December 2011 equates to 37.8% of the total number of biopsies during the last 10 year period.

Of patients with a HBV result, 11.8% ($n=83$) were HBV positive and 5.2% ($n=28$) of patients with a HCV result tested HCV positive. Of all patients biopsied during the study period 4.5% were HBV positive and 1.5% HCV positive. The proportion of patients with a positive HBV result decreased significantly from 22.2% during the first ten year period (1982-1991) and 24.5% during the second ten year period (1992-2001) to 9.6% between 2002 to 2011 ($p < 0.001$).

Only 17 patients (4.7% of HIV positive patients) were co-infected with HCV and HIV and 32 patients (8.8% of HIV positive patients) were co-infected with HBV and HIV.

During the study period as a whole there was an equal number of females and males that were HIV positive ($n=182$ each), however during the period 1992-2001 there was a greater proportion of female HIV positive patients (59.1% females vs. 40.9% males) while during the period 2002-2011 the HIV positive gender

distribution in essence reversed (50.4% males vs. 49.6% females) to closely resemble the 50/50 gender distribution of the total sample. The gender distribution for HBV positive patients were 33 (39.8%) females to 50 (60.2%) males and for HCV 11 (39.3%) females to 17 (60.7%) males.

Of the 364 HIV positive individuals only 7 patients were not black - 5 patients were coloured and 2 patients were white. The majority (64.0%) of patients that had a HIV positive result were young adults between the ages of 20 and 39 years ($p < 0.001$). The first patient that tested HIV positive was a 29 year old male in 1989 that was diagnosed with HIVAN on biopsy.

Table 3.8 summarizes the test results of patients tested for HIV, HBV and HCV over the total period under review as well as broken down into 10 year periods.

Table 3.8 Results of patients tested for HIV, HBV and HCV

	01/01/1982-31/12/1991	01/01/1992-31/12/2001	01/01/2002-31/12/2011	01/01/1982-31/12/2011
HIV positive (patient numbers)	1	22	341	364
% of patients with a retro status	0.8%	7.9%	39.8%	28.7%
HIV negative (patient numbers)	131	256	516	903
% of patients with a retro status	99.2%	92.1%	60.2%	71.3%
HBV positive (patient numbers)	14	12	57	83
% of patients with a HBV result	22.2%	24.5%	9.6%	11.8%
HBV negative (patient numbers)	49	37	535	621
% of patients with a HBV result	77.8%	75.5%	90.4%	88.2%
HCV positive (patient numbers)	0	4	24	28
% of patients with a HCV result	0.0%	44.4%	4.6%	5.2%
HCV negative (patient numbers)	5	5	502	512
% of patients with a HCV result	100.0%	55.6%	95.4%	94.8%

HIV (Human Immunodeficiency Virus); HBV (Hepatitis B Virus); HCV (Hepatitis C Virus).

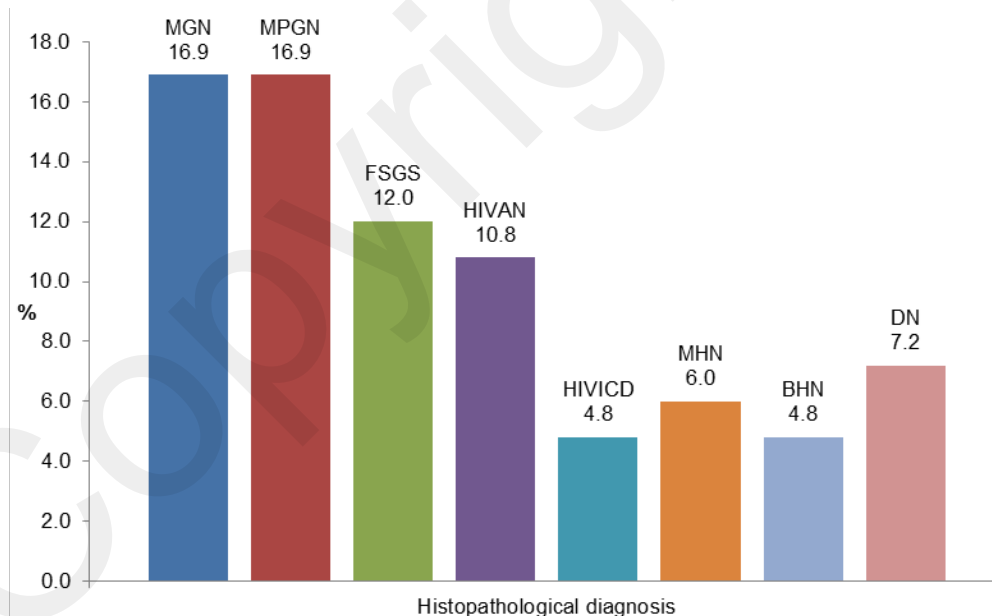
3.10 Infectious Related Diseases

Renal pathological changes secondary to an infectious process occurred in 299 (16.2%) of patients biopsied. A total of 83 (4.5%) patients had PIGN on biopsy.

The frequency of PIGN, as SGN, decreased significantly during the study period accounting for 16.7% (n=36) of SGNs between 1982 to 1991, 13.4% (n=24) between 1992 to 2001 and 4.4% (n=23) between 2002 to 2011 ($p<0.001$).

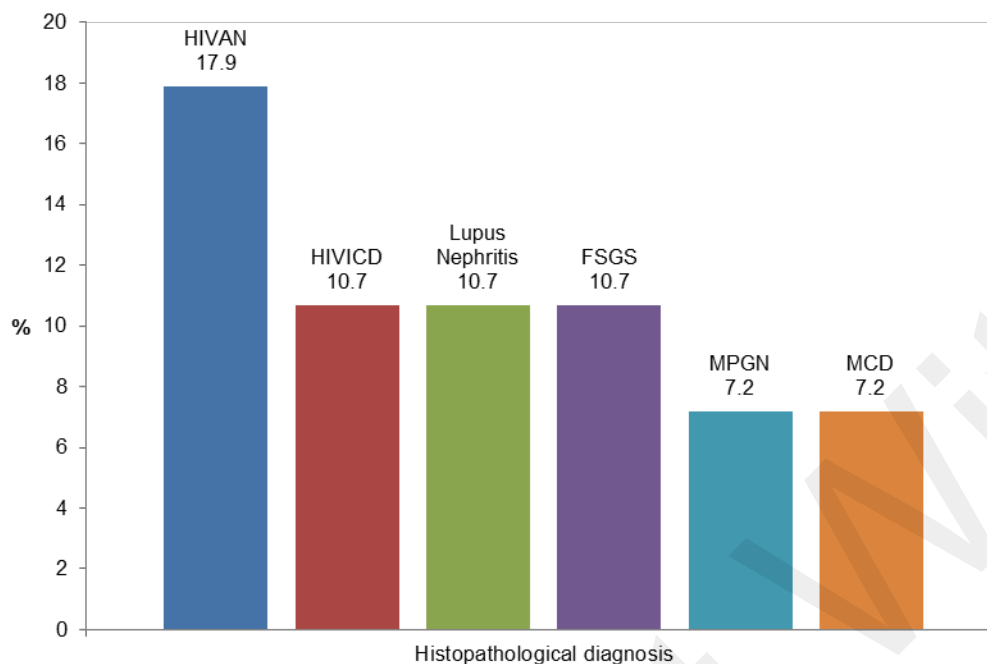
More males 56.6% (n=47) than females 43.3% (n=36) had PIGN ($p=0.202$). With regard to ethnicity, 96.4% (n=80) of the patients with PIGN were black and the other 3.6% (n=3) were coloured. PIGN occurred more frequently in younger patients, with 65.1% of patients with PIGN being younger than 40 years.

There was one HCV positive individual with cryoglobulinaemia and one with an immunotactoid GN. The most frequent histopathological findings for HBV positive patients are shown in Figure 3.7. The most frequent histological findings for HCV positive patients are shown in Figure 3.8.



MGN (Membranous glomerulopathy / glomerulonephritis); MPGN (Membranoproliferative glomerulonephritis); FSGS (Focal segmental glomerulosclerosis); HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); MHN (Malignant hypertensive nephroangiosclerosis); BHN (Benign hypertensive nephroangiosclerosis); DN (Diabetic Nephropathy).

Figure 3.7 Histopathological findings in HBV positive individuals



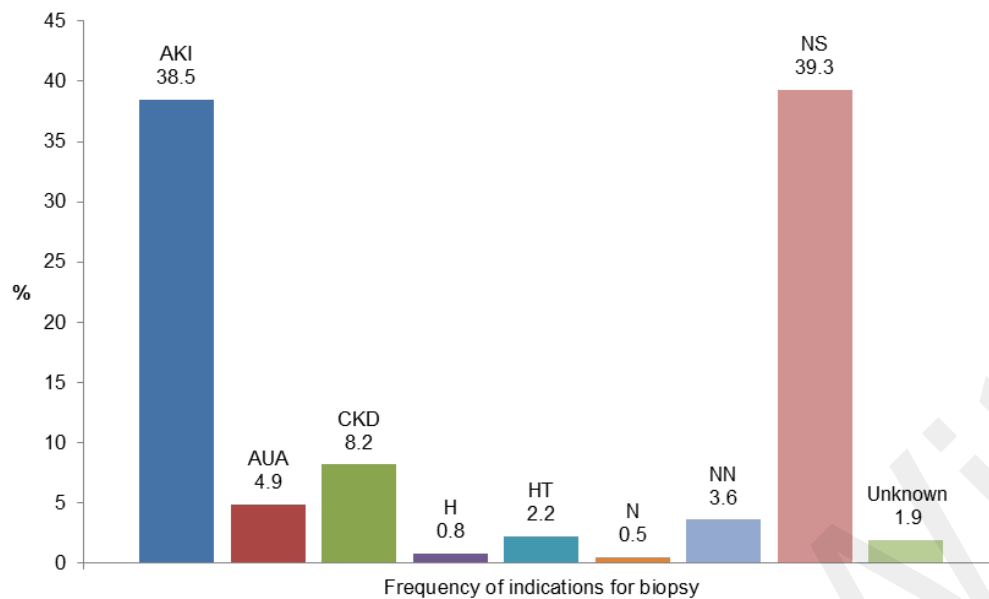
HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); FSGS (Focal segmental glomerulosclerosis); MPGN (Membranoproliferative glomerulonephritis); MCD (Minimal change disease).

Figure 3.8 Histopathological findings in HCV positive individuals

3.11 Indications for Biopsy, Histological Findings and Associations in HIV Positive Patients

The most frequent indications for biopsy in patients known to be HIV positive were NS (39.3%, n=143) and AKI (38.5%, n=140) which is similar to the two most frequent indications in HIV negative patients NS (50.6%, n=457) and AKI (16.9%, n=153) however, AKI as indication occurred more frequently in HIV positive individuals ($p<0.001$) and AUA ($p=0.002$), HT ($p=0.004$), NN ($p=0.027$) and NS ($p<0.001$) more frequently in HIV negative individuals.

The proportions of indications for renal biopsies in HIV positive patient are shown in Figure 3.9.



AKI (Acute kidney injury); AUA (Asymptomatic urine abnormalities); CKD (Chronic kidney disease); H (Haematuria); HT (Hypertension); N (Nephritic syndrome); NN (Nephritic nephrotic syndrome); NS (Nephrotic syndrome).

Figure 3.9 Biopsy indications in HIV positive individuals

The most frequent findings in HIV positive individuals with NS / nephrotic range proteinuria were HIVAN (27.3%, n=39), FSGS (17.5%, n=25) and MGN (15.4%, n=22) compared to FSGS (19.5%, n=89) and MGN (19.5%, n=89) and lupus nephritis (17.1%, n=17.1%) in HIV negative individuals.

The most frequent indications for biopsy in patients with HIVAN were AKI (52.1%), NS (32.8%) and CKD (9.2%) and for patients with HIV-ICD NS (34.9%), AKI (25.6%) and AUA (14.0 %).

In HIV positive individuals HIVAN (32.7%), HIV-ICD (11.8%) and FSGS (11.3%) were the most frequent findings compared to patients known to be HIV negative in whom lupus nephritis (21.7%), FSGS (13.0%) and MGN (11.3%) were the most frequent findings.

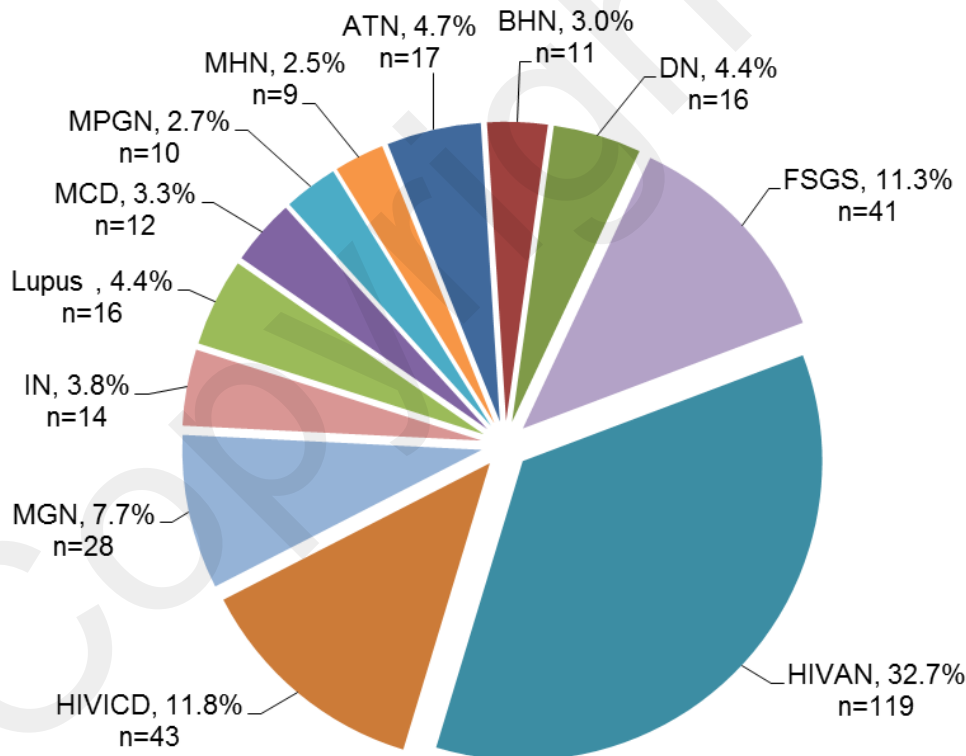
In the present study the most frequent PGNs in HIV positive and negative individuals were FSGS, MGN and MPGN - a comparison of the proportions of PGN in HIV positive and negative individuals are shown in Table 3.9.

The 12 major histological findings in HIV positive individuals are shown in Figure 3.10.

Table 3.9 PGNs in patients with known HIV results

	HIV Negative	HIV Positive
CresGN	0.8% (n=3)	0.0% (n=0)
FSGS	29.3% (n=112)	43.8% (n=35)
IgAN	3.4% (n=13)	1.3% (n=1)
IgM	0.0% (n=0)	1.3% (n=1)
MCD	13.9% (n=53)	11.3% (n=9)
MGN	25.7% (n=98)	28.8% (n=23)
MPGN	19.9% (n=76)	12.5% (n=10)
MsPGN	7.1% (n=27)	1.3% (n=1)
ProlifGN	0.0% (n=0)	0.0% (n=0)

CresGN (Crescentic glomerulonephritis); FSGS (Focal segmental glomerulosclerosis); IgAN (Immunoglobulin A nephropathy); IgM (Immunoglobulin M nephropathy); MCD (Minimal change disease); MGN (Membranous glomerulopathy / glomerulonephritis); MPGN (Membranoproliferative glomerulonephritis); MsPGN (Mesangioproliferative glomerulonephritis); ProlifGN (Proliferative glomerulonephritis).



ATN (Acute tubular necrosis); BHN (Benign hypertensive nephroangiosclerosis); DN (Diabetic Nephropathy); FSGS (Focal segmental glomerulosclerosis); HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); MGN (Membranous glomerulopathy / glomerulonephritis); IN (Interstitial nephritis); Lupus (Lupus Nephritis); MCD (Minimal change disease); MPGN (Membranoproliferative glomerulonephritis); MHN (Malignant hypertensive nephroangiosclerosis).

Figure 3.10 Histopathological findings in HIV positive individuals

T1D were found in 9.1% (n=33) of HIV positive biopsies compared to 7.5% (n=68) of HIV negative biopsies.

When comparing histological findings between patients that tested HIV positive versus HIV negative, only HIV specific conditions (HIVAN and HIV-ICD) were found significantly more frequent in HIV positive than negative individuals but lupus nephritis ($p<0.001$), MHN ($p=0.001$), MPGN ($p<0.001$) and MsPGN ($p=0.003$) were found more frequently in HIV negative individuals.

There was a statistically significant increase in the number of patients diagnosed with HIVAN and HIV-ICD over the entire 30 years ($p<0.001$), a single HIV positive patient was diagnosed with HIVAN between 1 January 1982 – 31 December 1991, 10 patients between 1 January 1992 – 31 December 2001 and 108 patients between 1 January 2002 – 31 December 2011. All patients that were diagnosed with HIV-ICD were biopsied between 2002 and 2011.

The female to male ratio for patients with HIVAN were 51.2% to 48.8% and for HIV-ICD, 46.5% to 53.5%, the majority of patients with HIVAN and HIV-ICD were young adults with 73.9% and 67.4% being younger than 40 years old.

When looking at cluster of differentiation 4 (CD4) counts, creatinine levels and PCRs, a total of 265 of the HIV positive individuals had CD4 counts recorded, the median CD4 count was 195 cells/ μ l and the lowest and highest CD4 counts were 1 cells/ μ l and 1605 cells/ μ l. A CD4 count of ≤ 50 cells/ μ l was associated with HIVAN as diagnosis ($p<0.001$).

The median creatinine for biopsied HIV positive patients were 316 μ mol/l and the median PCR 0.61 grams/mmol which is in the nephrotic range of proteinuria.

The median CD4 count, creatinine and PCR for different histopathological diagnosis in HIV positive individuals are shown in Table 3.10.

Table 3.10 CD4 counts, Creatinine levels and PCR for various histopathological diagnoses

Histopathological diagnosis	Median CD4 count cells/ μ l (IQR)	Median Creatinine μ mol/l (IQR)	Median PCR grams/mmol (IQR)
HIVAN	92 (28 - 196)	539 (279 - 799)	0.92 (0.37 - 1.44)
HIV-ICD	198 (85 - 297)	141 (76 - 435)	0.31 (0.06 - 0.70)
FSGS	434 (174 - 566)	104 (80 - 331)	0.83 (0.40 - 1.38)
MGN	360 (197 - 491)	89 (74 - 220)	0.78 (0.46 - 0.99)
MCD	165 (77 - 226)	119 (76 - 175)	0.83 (0.26 - 1.51)
MPGN	380 (316 - 435)	207 (76 - 333)	0.99 (0.28 - 1.20)

IQR (Interquartile Range).

HIVAN (Human Immunodeficiency Virus associated Nephropathy); HIV-ICD (Human Immunodeficiency Virus Immune complex disease); FSGS (Focal segmental glomerulosclerosis); MGN (Membranous glomerulopathy / glomerulonephritis); MCD (Minimal change disease); MPGN (Membranoproliferative glomerulonephritis).

3.12 Lupus Nephritis

A total of 282 patients (15.3% of all biopsies) were found to have lupus nephritis on biopsy from 1 January 1982 to 31 December 2011. Lupus nephritis was the sole contributor to SD and accounted for 31.0% of all SGNs.

The most frequent clinical indications for renal biopsies in patients with lupus nephritis were AUA (42.6%), NS (38.3%) and AKI (11.7%). For patients who had Class 5 lupus nephritis on biopsy (alone or with other changes) the most frequent indications for biopsy were NS (46.0%) and AUA (40.7%), and for patients with either focal or diffuse proliferative changes on biopsy (alone or in conjunction with other changes) the most frequent indications were NS (38.6%), AUA (38.0%) and AKI (14.5%).

Class 5 lupus nephritis alone (25.9%) was the most frequent ISN/RPS lupus nephritis Class found and was present in a total of 53.2% (n=150) of biopsies with lupus nephritis.

Lupus nephritis as diagnosis occurred significantly more frequent in females than males (89.4% vs. 10.6%; $p<0.001$), but no statistically significant association between ethnicity and lupus nephritis as a diagnosis was found.

Lupus nephritis was more frequently found in young adults with 14.5% (n=41) of patients being younger than 20 years old, 65.2% (n=184) between 20 – 39 years, 17.7% (n=50) between 40-59 years and only 1.1% (n=3) of patients being 60 years and older.

Lupus nephritis was found significantly more frequent in 20-39 year olds than in individuals of 40 years and older ($P<0.001$).

The different classes of lupus nephritis on biopsy are summarized in Table 3.11.

Table 3.11 Proportions of ISN/RPS lupus nephritis classes on biopsy

Class	01/01/1982-31/12/1991	01/01/1992-31/12/2001	01/01/2002-31/12/2011	01/01/1982-31/12/2011
1	2.2% (n=1)	0.0% (n=0)	2.0% (n=3)	1.4% (n=4)
2	6.5% (n=3)	8.0% (n=7)	9.4% (n=14)	8.5% (n=24)
2+5	10.9% (n=5)	5.7% (n=5)	0.7% (n=1)	3.9% (n=11)
3	17.4% (n=8)	23.0% (n=20)	12.8% (n=19)	16.7% (n=47)
3+5	13.0% (n=6)	14.9% (n=13)	16.1% (n=24)	15.2% (n= 43)
4	10.9% (n=5)	18.4% (n=16)	21.5% (n=32)	18.8% (n=53)
4+5	17.4% (n=8)	9.2% (n=8)	4.7% (n=7)	8.2% (n=23)
5	19.6% (n=9)	19.5% (n=17)	31.5% (n=47)	25.9% (n=73)
6	2.2% (n=1)	1.1% (n=1)	0.7% (n=1)	1.1% (n=3)
Unclass	0.0% (n=0)	0.0% (n=0)	0.7% (n=1)	0.4% (n=1)

4. DISCUSSION

4.1 Study Sample

This study included a total of 1848 native adequate renal biopsies over a 30 year period from 1 January 1982 to 31 December 2011 and constituted the largest data sample of renal biopsy reports published to date from South Africa. The sample in this study was predominantly of black ethnicity (96.4%) compared to the other studies from South Africa, for instance, Okpechi, *et al* (2011) in which coloured patients (53.7%) followed by black patients (42.4%) were the most frequent ethnicities and Jansen van Rensburg, *et al* (2010) where black patients accounted for 57.2% of the study population and white patients for 35.9%. As such the histopathological patterns in this study significantly add to our knowledge regarding the patterns of renal disease in South Africa and Sub-Saharan Africa as a whole where the majority of patients are of black ethnicity.

The sample in this study includes a fairly large number of biopsy reports from HIV positive individuals, namely 364 patients, which equates to 19.7% of all biopsies. and is much higher than those from previous studies from South Africa – Swanepoel & Okpechi (2011) included 262 HIV positive patients in their Cape Town study and in studies that exclusively focussed on patients with HIV - Wearne, *et al* (2011) included 221 HIV positive renal biopsies and Han, *et al* (2006) included 30 HIV positive biopsies.

There is an almost equal distribution between females (50.2%) and males (49.8%) biopsied in the study sample, which is similar to the reported gender distribution according to the 2013 mid-year statistics for South Africa which

indicates just over 51% of the South African population to be female (Statistics South Africa, 2013).

The majority of patients in the study were young adults with a mean age of 33.5 $\pm$ 12.6 years, in fact, 68.5% of patients biopsied were younger than 40 years of age which closely mirrors that reported by Okpechi, *et al* (2011) who reported 61.8% of patients younger than 40 years of age.

4.2 Indications for Renal Biopsy

When examining the indications for renal biopsy the results from this study are very similar to data reported from Cape Town by Okpechi, *et al* (2011). In both studies NS, AKI and AUA were the most frequent indications for renal biopsy; accounting for 47.7%, 19.8% and 8.1% respectively in the present study and 52.5%, 21.3% and 13.6% in the Cape Town study. When referring to Table 4.1 it is clear that NS is the most frequent indication for biopsy in South Africa (Jansen van Rensburg, *et al.*, 2010; Okpechi, *et al.*, 2011) as well as in the majority of studies published from Africa (Barsoum & Francis, 2000; Abdou *et al.*, 2003; Aatif, *et al.*, 2012; Nadium *et al.*, 2013), the Middle East (Wahbeh, *et al.*, 2008; Ossareh, *et al.*, 2010), Asia (Mubarak, *et al.*, 2009; Zhou, *et al.*, 2009; Das, *et al.*, 2011; Hsiao, *et al.*, 2012; Golay, *et al.*, 2013) America (Arias, *et al.*, 2009; Polito, *et al.*, 2010) and parts of Europe (Rivera, *et al.*, 2002; Naumovic, *et al.*, 2009).

Exceptions to this pattern are Belgium (Mesquita, *et al.*, 2011), Finland (Wirta, *et al.*, 2008) and Italy (Gesualdo, *et al.*, 2004) where AUA is the most frequent indication for biopsy which is most likely due to early detection of disease in these

Table 4.1 Comparative summary of published biopsy reports

Country	Year	Author and year of publication	Most frequent indication	Most frequent group	Most frequent PGN	Most frequent SGN
Africa:						
RSA – CHBAH (This study)	2014	Vermeulen	NS (47.7%)	SGN (49.3%)	FSGS (29.6%)	Lupus Nephritis (31%)
RSA – CPT	2011	Okpechi, <i>et al</i>	NS (52.5%)	SGN (49.0%)	MPGN (20.4%)	Lupus Nephritis (39%)
RSA - Bloemfontein	2010	Jansen van Rensburg, <i>et al</i>	NS	N/A	FSGS	N/A
Egypt	2000	Barsoum & Francis	NS (31.9%)	N/A	FSGS (22.6%)	N/A
Morocco	2012	Aatif, <i>et al</i>	NS (60.3%)	PGN (52%)	MCD (26%)	Lupus Nephritis (45%)
Oman	2013	Dawood, <i>et al</i>	N/A	SGN	FSGS	Lupus Nephritis (36.1%)
Senegal	2003	Abdou, <i>et al</i>	NS (67%)	PGN (69.5%)	FSGS (47%)	Lupus Nephritis (55.5%)
Sudan	2013	Nadium, <i>et al</i>	NS (46.5%)	PGN (85.5%)	FSGS (29.6%)	N/A
Middle East:						
Iran	2010	Ossareh, <i>et al</i>	NS (57.4%)	PGN (74.8%)	MGN (35.8%)	Lupus Nephritis (64.3%)
Jordan	2008	Wahbeh, <i>et al</i>	NS (51.6%)	PGN (59.4%)	FSGS	Lupus Nephritis
Europe:						
Belgium	2011	Mesquita, <i>et al</i>	AUA (53.5%)	SGN (39.9%)	FSGS (30.3%)	IMGN (32.3%)
Finland	2008	Wirta, <i>et al</i>	AUA (38.7%)	PGN	IgAN (34.9%)	N/A
France	2004	Simon, <i>et al</i>	CKD (36%)	PGN	IgAN (73.4%)	N/A
Italy	2004	Gesualdo, <i>et al</i>	AUA	PGN (64.3%)	IgAN (34.5%)	Immune-med GN (IMGN)
Serbia	2009	Naumovic, <i>et al</i>	NS (53.6%)	PGN (64.2%)	MsPGN – non IgA (25.1%)	Lupus Nephritis (75.6%)
Spain	2002	Rivera, <i>et al</i>	NS (35.2%)	PGN	IgAN (17.2%)	Lupus Nephritis
UK:						
North Ireland	2009	Hanko, <i>et al</i>	N/A	PGN (49%)	IgAN (39%)	N/A
Asia:						
China	2012	Hsiao, <i>et al</i>	NS (52%)	PGN (55%)	MGN (31.7%)	Lupus Nephritis (53.2%)
E-India	2013	Golay, <i>et al</i>	NS (61.6%)	PGN (79.13%)	FSGS	Lupus Nephritis (73.38%)
S-India	2011	Das, <i>et al</i>	NS (49%)	PGN (69.1%)	MCD (21.8%)	Lupus Nephritis (80.1%)
Japan	2011	Sugiyama, <i>et al</i>	Chronic nephritic syndrome (48.2%)	PGN	IgAN (27.6%)	DN
Korea	2009	Chang, <i>et al</i>	N/A	PGN	IgAN (28.3%)	Lupus Nephritis (74%)
Northern China	2009	Zhou, <i>et al</i>	NS	PGN (63.3%)	IgAN (54.5 %)	N/A
Pakistan	2011	Mubarak, <i>et al</i>	NS (49.9%)	PGN (73%)	FSGS (29%)	Lupus Nephritis (44.1%)
Americas:						
Brazil	2010	Polito, <i>et al</i>	NS (39%)	PGN (51%)	FSGS (24.6%)	Lupus Nephritis (45.5%)
Colombia	2009	Arias, <i>et al</i>	NS	PGN (76.2%)	FSGS (37.7%)	Lupus Nephritis (90.9%)
USA - Minnesota	2006	Swaminathan, <i>et al</i>	N/A	N/A	IgAN (22%)	N/A
Australia:						
Australia	2001	Briganti, <i>et al</i>	N/A	N/A	IgAN (34.1%)	N/A

first world countries, France (Simon, *et al.*, 2004) in which CKD was the most common, and Japan (Sugiyama, *et al.*, 2011) in which chronic nephritic syndrome is the most frequent biopsy indication, most likely due to the high prevalence of IgAN in this part of the world.

The three most frequent histological findings for patients with NS in this study were FSGS (19.8%), MGN (19.2%) and lupus nephritis (12.3%). In contrast to the findings in this study, the study published by Okpechi, *et al* (2010) from Cape town evaluating nephrotic range proteinuria/NS in 294 black patients, identified the most frequent causes of NS as HIVAN (25.2%), MPGN (7.8%) and lupus nephritis (7.8%) while Seedat (1992) from KZN reported MPGN to be the most frequent cause of NS in black patients (47.0%) followed by MGN (25.0%).

In this study the most frequent pathological findings in patients biopsied for AKI were HIVAN (16.9%), ATN (15.0%) and lupus nephritis (9.0%) which is similar to findings from Cape Town (Okpechi, *et al.*, 2010) in which ATN (23.4%), HIVAN (15.0%) and lupus nephritis (14.2%) were the most frequent findings in patients biopsied for AKI.

Lupus nephritis was the most frequent finding (80.0%) in patients biopsied for AUA, most likely reflecting good surveillance of the SLE / Rheumatology clinic at CHBAH and early referral of patients with suspected lupus nephritis for biopsy. As noted before, in developing countries patients with asymptomatic renal disease are rarely referred to a nephrology unit (Jansen van Rensburg, *et al.*, 2010; Okpechi *et al.*, 2011).

The most frequent indications for biopsy in HIV positive individuals in this study were NS (39.3%), AKI (38.5%) and CKD (8.2%), other South African studies

looking at biopsies in HIV positive individuals were largely performed for varying degrees of proteinuria rather than describing different indications for biopsies in these patients (Han, *et al.*, 2006; Okpechi, *et al.*, 2010).

4.3 Comparison of Geographic Variation in Pathology

In this study SGN (49.3%) was more common than PGN (39.7%) over the 30 year study period. As can be seen from Table 4.1 the finding of SGN as the most frequent nephropathy has only been found in a few other studies – Okpechi, *et al* (2011) from Cape Town and Mesquita, *et al* (2011) from Belgium.

The most frequent PGNs in this study were FSGS (29.6%), MGN (25.7%) and MPGN (18.1%) – with reference to Table 4.1 this finding is in keeping with other studies from Africa (Barsoum & Francis, 2000; Abdou *et al.*, 2003; Jansen van Rensburg, *et al.*, 2010; Dawood, *et al.*, 2013; Nadium *et al.*, 2013) that report FSGS as the most frequent PGN. The high frequency of FSGS in the study sample may be explained by the presence of a possible genetic predisposition in the predominantly black patient population – similar to that shown in African Americans where the presence of a single APOL1 risk allele (G1 or G2) incurs a 17 fold higher odds for FSGS and a 29 fold higher odds for HIVAN (Kopp, *et al.*, 2011). Further research is however required to adequately explore this hypothesis and to clarify the reasons for the higher frequency of FSGS.

IgAN accounted for only 3.5% of PGN in this study in contrast to IgAN as the most frequent PGN in most of Europe (Rivera, *et al.*, 2002; Gesualdo, *et al.*, 2004; Simon, *et al.*, 2004; Wirta, *et al.*, 2008), areas in Asia (Chang, *et al.*, 2009; Zhou, *et al.*, 2009; Sugiyama, *et al.*, 2011), USA (white Americans) (Swaminathan, *et al.*,

2006) and Australia (Briganti, *et al.*, 2001) – see Table 4.1. It is possible that IgAN may be under represented in this study because of the ethnic distribution of the study sample and since patients with isolated haematuria (least frequent indication for biopsy in this study at 1.7%) are not frequently subjected to a renal biopsy. The low frequency of IgAN in this study does however correlate with the frequency of IgAN as reported by other South African studies. In the Cape Town study IgAN accounted for 5.8% of PGN (Okpechi, *et al.*, 2010) while in KZN, Seedat, *et al* (1988) reported IgAN in only 2 (0.8%) black patients and 13.3% of Indian patients.

Overall, IgAN appears to be rare in patients of African descent – this holds true outside of Africa as well, Nair & Walker (2006) found IgAN to be the most frequent PGN and cause of ESRD in young Caucasian American adults between 20-39 years, but found IgAN rarely occurred in African Americans in whom FSGS was the most frequent PGN.

The most frequent SGN in this study was lupus nephritis (31.0%) followed by HIVAN (13.3%) and MHN (12.5%). This is similar to most other areas around the world and South Africa (see Table 4.1).

Focussing on lupus nephritis, this study found the most frequent ISN/RPS histological subtypes of lupus nephritis to be Class V (25.9%) followed by Class IV (18.8%). The frequencies of Class I and Class II lupus nephritis may be under represented in general as most patients with these two classes of lupus nephritis may not routinely be biopsied due to inactive urine sediment, proteinuria <1g/day and a normal creatinine (Appel, *et al.*, 2012). In comparison, Tikly, *et al* (1996) in an earlier study in black SLE patients from CHBAH found lupus nephritis in 48.6% of patients with WHO Class V lupus nephritis (46.2%) as the most frequent histological class, followed by Class III (26.9%). Okpechi, *et al* (2012) found

ISN/RPS histological subtypes Class III and IV (20.7% each) to occur most frequently in their lupus nephritis study in Cape Town.

According to Naicker (2009) the prevalence of DN in South Africa is estimated at 14-16% but in the present study DN accounted for only 6.6% of SGNs and 3.2% of all biopsies. This finding is similar to that of Mesquita, *et al* (2011) who reported that although DN is estimated to cause 45% of ESRD in Belgium, only 5.8% of all biopsies in their biopsy series were accounted for by DN. Similarly, DN accounted for only 1.8% of biopsies in data from Brazil (Polito, *et al.*, 2010), 4.8% in Japan (Sugiyama, *et al.*, 2011) and 1.2% in India (Das, *et al.*, 2011).

The low frequency of DN found on renal biopsy may be due to the fact that patients with suspected DN are only biopsied if there is some uncertainty regarding the diagnosis and non-diabetic renal disease is expected – this is consistent with clinical practice in South Africa and other areas around the world (Ghani, *et al.*, 2009; Okpechi, *et al.*, 2011). However, the recent study by Wilfred, *et al* (2013) emphasizes the fact that type 2 diabetics with atypical disease should be biopsied, in their biopsy series non diabetic renal disease with or without DN occurred in 68.8% of type 2 diabetics with atypical presentations with T1D in 73.4% and glomerular disease in 26.6% of patients with MGN as most frequent glomerular disease.

In this study T1D was present in 7.4% of all biopsies which is less than reported from other areas in South Africa, in Bloemfontein T1D accounted for 22.5% of patients with a pathological diagnosis (Jansen van Rensburg, *et al.*, 2010) and 10.8% of biopsies in the Okpechi, *et al* (2011) study from Cape town. T1D was found to have a similar prevalence as in the studies from Belgium 6.7% (Mesquita, *et al.*, 2011) and India 6.7% (Das, *et al.*, 2011).

4.4 Patterns of Renal Disease in HIV

The first patient in this study that was reported as HIV positive was a patient with HIVAN in 1989 – 2 years after the first patient that tested HIV positive at CHBAH in 1987 (Karstaedt, 1992) and 5 years after the first published association of AIDS/HIV with FSGS by Roa, *et al* (1984) and Pardo, *et al* (1984) from the USA. This also precedes the first published case of HIVAN in South Africa by Bates, *et al* (1994) by 5 years. The proportion of HIV positive patients in the present study increased over the study period ($p < 0.001$), 37.8% of all biopsies performed between 1 January 2002 and 31 December 2011 were on HIV positive patients, which is higher than the highest reported antenatal HIV seroprevalence in Gauteng between 2002 and 2011 which was 33.1% for 2004 (Health Systems Trust, 2013)

The most frequent histological findings in this study for HIV positive individuals were HIVAN (32.7%), HIV-ICD (11.8%) and FSGS (11.3%). TID did not occur as frequently in HIV positive individuals in this study as in other studies and accounted for 9.1% of pathologies in HIV positive individuals with ATN (4.7%) and IN (3.8%). Similar to this study, pathology patterns in HIV positive individuals reported from other areas in South Africa also found HIVAN to be the most frequent histopathological finding in HIV positive individuals accounting for 55.3% of biopsies from Groote Schuur Hospital in Cape Town (Swanepoel & Okpechi; 2011) and 83% of biopsies from KZN (Han, *et al*.; 2006) followed by ATN (8.0%) and ESKD (7.2%) in Cape town and IN (10.0%) and MPGN (7.0%) in KZN. Berliner, *et al* (2008) from Baltimore in the USA reported their most frequent histopathology findings in HIV positive individuals as HIVAN (35%), non-collapsing FSGS (22%) and AIN (7.9%).

In the current study only the two HIV specific conditions (HIVAN and HIV-ICD) occurred statistically significantly more frequently in HIV positive than HIV negative individuals. In contrast, MPGN ($p<0.001$), MsPGN ($p=0.003$), MHN ($p=0.001$) and lupus nephritis ($p<0.001$) occurred in higher proportions in HIV negative than HIV positive individuals.

In the present study HIVAN was associated with a CD4 count of ≤ 50 cells/ μ l ($p<0.001$) and a median CD4 count of 92 cells/ μ l which fits with Lescure, *et al* (2012) who report that in their study the median CD4 count in patients with HIVAN were 74 cells/ μ l and Berliner, *et al* (2008) who found a CD4 count > 200 cells/ μ l to be a strong negative predictor of HIVAN, in contrast Wearne, *et al* (2012) in an HIV series from Cape Town, also with HIVAN (57.3%) as the most frequent finding, found that the median CD4 count was the lowest in patients with conditions other than HIVAN / HIV-ICD.

It is noteworthy that in the abovementioned studies there were differences found in respect of the apparent effects of ARVs on the frequency and prognosis of patients with HIVAN. In the study by Berliner, *et al* (2008) 29.6% of all biopsied patients were on ARVs – the authors found that the occurrence of HIVAN was much lower in patients on ARVs (22%) compared to ARV naïve patients (46%) and that patients with HIVAN had a significantly higher mortality rate compared to patients without HIVAN. Similarly Lescure, *et al*. (2012) found that the frequency of HIVAN decreased over time since the introduction of HAART. However, in the study by Wearne, *et al* (2012) 37.5% of all patients biopsied were on ARVs with the majority of patients (61.1%) on ARVs having HIVAN on biopsy – in these patients ARVs still appeared to reduce the overall mortality of patients with any features of HIVAN by 57%.

4.5 Change of Patterns in Renal Disease over Time

When looking at changes in the frequencies of various pathologies over the 30 year period a statistically significant increase in SGN ($p<0.001$) and decrease in PGN ($p<0.001$) occurred during the study period which is likely largely explained by the statistically significant increase in ID ($p<0.001$) during the study period, which in turn is likely linked to the prevalence of HIV related diseases during the last 10 year period between 2002 and 2011.

Despite the PGN decrease overall, between 1982 and 1991 the PGN frequency was higher than that for SGN (48.1% vs. 37.7% of biopsies) which is likely due to a relatively lower frequency of lupus nephritis during this time period as well as the lower frequency of HIV associated diseases during that 10 year period – only a single a HIV positive biopsy was reported during this time.

Statistically significant increases from the first ten year period (1982–1991) to the second ten year period (1992–2001) occurred for both DN ($p=0.049$) and lupus nephritis ($p<0.001$). Between the same time periods primary MCD, BHN and MHN decreased statistically significantly ($p=0.006$, $p<0.001$ and $p=0.044$).

From the second (1991–2002) to the third ten year period (2002–2011) there was a statistically significant increase in primary FSGS ($p=0.002$). Various other studies (Braden, *et al.*, 2000; Das, *et al.*, 2011; Swaminath *et al.*, 2006) also found an increase in the frequency of FSGS in recent years.

During the 30 year study period there was a statistically significant increase in HIVAN and HIV-ICD ($p<0.001$ and $p<0.001$). Similarly an increase in HIVAN was also described in Cape Town by Okpechi, *et al* (2011) while Lescure, *et al* (2012) in France reported a decrease in HIVAN and increase frequency in classic FSGS

between 2004 to 2007 in their HIV positive patients. The differences between South Africa and France is most likely secondary to the earlier availability of antiretroviral therapy in France and health system differences between developing and developed countries – the rollout of antiretroviral therapy in South Africa only started in 2004 (van Dyk 2010).

Statistically significant decreases in AMY ($p=0.01$), ESKD ($p<0.001$), and PIGN ($p<0.001$) was found during the 30 year study period. As in this study, a decrease in the frequency of PIGN has been reported for developed as well as developing countries (Nasr, *et al.*, 2013) and is most likely explained by improvement in living conditions as well as antibiotic availability at primary health care levels. In comparison Zhou, *et al* (2009) found that in China PGN remained the most frequent finding in their study from 1993-2007 with IgAN being the most common PGN but they found an increase in the frequency of MGN and FSGS in young adults (14-24 year olds) and a decrease in MsPGN (non-IgAN).

4.6 Renal Disease and Gender

When looking at gender differences in this study PGN ($p<0.001$), VD ($p=0.018$) and T1D ($p=0.002$) were statistically significantly more frequent in males than in females while SD ($p<0.001$) and combined SGNs ($p<0.001$) were more frequent in females. The male to female frequencies of PGN and SGN in this series are similar to findings reported in Brazil (Polito, *et al.*; 2010), Belgium (Mesquita, *et al.*, 2011).and in Italy (Gesualdo, *et al.*; 2004). The high frequency of SGN in females in this study is likely due to the prevalence of lupus nephritis which is more frequent in females ($p <0.001$).

Lupus nephritis is a disease of primarily young females and is found more frequently in patients of African descent in whom it has a worse prognosis (Borchers, *et al.*, 2010). Okpechi, *et al* (2012) from Groote Schuur Hospital in Cape Town found lupus nephritis to occur more frequently in patients of mixed ancestry – 79.3% (coloured patients) than in black patients – 17.5% with females (84.7%) being affected more than males at a mean age of 31 ± 11.6 years. Tikly, *et al* (1996) at CHBAH also showed a female dominance (92.8%) with a mean age of 35.1 years. In the present study lupus nephritis occurred more frequently in females than males ($p < 0.001$) with the odds of a female having lupus nephritis being 11 times as high as the odds for a male having lupus nephritis. Lupus nephritis was also statistically significantly more frequent in young adults between 20-39 years than individuals older than 40 years ($p < 0.001$). Unlike age and gender, no meaningful racial association could be made for lupus nephritis but this is most likely due to the small number of non-black patients in this study which did not allow for adequate comparison based on ethnicity.

In this study only lupus nephritis occurred more frequently in females than males but males had a statistically significant higher frequency than females of ATN ($p = 0.002$), BHN ($p = 0.014$), ESKD ($p = 0.017$), IgAN ($p = 0.046$) and idiopathic MPGN ($p < 0.001$) with the only comparable gender frequency for MPGN reported in the Cape Town study (Okpechi, *et al.*, 2011) where MPGN, MGN and PIGN occurred more frequently in males. While Silbiger & Neugarten (2008) reported the prevalence for FSGS, MGN and IgAN to be slightly higher in adult males, in the present study only IgAN showed a similar gender association.

4.7 Renal Disease and Ethnicity

In view of the small number of coloured, Indian and white patients in the sample, the statistical significance of racial differences in pathological findings could not be determined but differing racial patterns are suggested. In this study, SGN occurred more frequently than PGN in black patients (49.2% vs. 39.6%) – a similar pattern was evident for coloured patients (75.9% vs. 24.1%). SGN and PGN were found at equal frequencies (45.5%) in Indian patients while in white patients PGN (61.5%) occurred more frequently. For both black and coloured patients the most frequent histopathological finding was lupus nephritis (15.1% and 27.6% respectively), and in Indian patients lupus nephritis occurred at the same frequency as FSGS (27.3%), while in white patients both FSGS and MGN were the most frequent findings at 19.2% each.

The high frequency of SGNs in the black and coloured patients in this study (49.2% and 75.9% respectively) are most likely secondary to the high frequency of lupus nephritis in both groups as well as HIV related diseases (ID) in the black patients.

In this study FSGS was the most frequent PGN in black, Indian and white patients while MCD was the most frequent PGN in coloured patients. Lupus nephritis was the most frequent SGN in this study for all ethnicities except for white patients in whom MHN (37.5% n=3) occurred at a higher frequency than lupus nephritis (25% n=2).

The results from this study differ somewhat from previously published studies from South Africa. According to results by Seedat, *et al* (1988) in KZN, MPGN was the most common PGN in black patients (35.7%) and MsPGN the most common

in Indian patients (26.7%). Okpechi, *et al* (2011) found the most frequent PGN in black and coloured patients to be MPGN (20.6% and 20.7% respectively) followed by MsPGN (17.7%) in black patients and MGN (19.9%) in coloured patients; while in white patients, MsPGN (27.8%) was the most frequent PGN followed by MGN (22.2%). They also found FSGS to occur more frequently in black patients than other ethnicities. The most frequent SGN found in black patients by Okpechi, *et al* (2011) was infectious related glomerular diseases (57.9%) with HIVAN as main contributor, followed by lupus nephritis (15.9%). In both patients of coloured and white ethnicity lupus nephritis was the most frequent SGN at 59.1 % and 38.1% respectively followed by VD.

While the present study results differed from other local studies, the aforementioned findings of FSGS and MGN as the most frequent PGN in black patients and MGN and FSGS in white patients are similar to that of Korbett, *et al* (1996) from Chicago, USA who reported the most frequent PGN in black patients as FSGS (57%), MGN (24%), MCD (14%), MPGN (2%) and IgAN (2%) while for white patients MGN (36%), FSGS (23%), MCD (20%) and IgAN (8%) were most frequent. They also found a statistically significant increase in the frequency of FSGS in black patients over time from 39% to 64% between 1974 and 1984 as well as between 1985 and 1994.

4.8 Renal Disease and Age

When looking at the association of age and histological findings for patients biopsied for NS, this study found that in young adults (<20 years) the most frequent pathology was FSGS (29.1%) and in all other age groups, MGN was the

most frequent finding. The finding of MGN as the dominant cause for NS in the elderly is similar to Mohamed & John (2011) who report MGN to cause 40% of NS in the elderly.

In the present study the most frequent PGN across all age groups was FSGS for the four different age groups but for patients between 20-39 years old and those 60 years and older MGN occurred at the same frequency. In most parts of the world the most frequent PGNs are IgAN and MGN (see Table 4.1). Non South African studies reporting on age related frequency differences report the most frequent PGNs to be either IgAN or FSGS in young adults and MGN in the elderly (Pesce & Schena, 2010). Similar to the present study, MGN as most frequent PGN in the elderly is also reported from France (Simon, *et al.*, 2004), Ireland (Brown *et al.*, 2012), Brazil (Polito *et al.*, 2010) and Cape Town, South Africa (Okpechi, *et al.*, 2011). Unlike the present study, Okpechi, *et al* (2011) found MPGN to be the most frequent PGN in patients younger than 60 years.

4.9 Limitations

Due to the retrospective nature of this study it is prone to some limitations. One issue pertains to the potential completeness of the data. Missing information due to inconsistencies in the recording of data by different personnel who conducted biopsies at CHBAH over time as well as biopsy records that might have been misplaced make it possible that some biopsies or associated data were not included in the data set. However, every effort was made to locate all relevant records and data, including the scouring of archival patient records only contained in hard copy paper format.

Some renal diseases could be under represented in the data because they are not routinely biopsied. DN and isolated microscopic haematuria that may be due to IgAN are two such conditions. Patients that present with advanced renal failure with contra-indications to renal biopsy may result in under representation of the true frequency of various pathologies including HIVAN and HIV-ICD.

The data may be skewed by the high referral rate for biopsies of SLE patients by the division of Rheumatology at CHBAH.

As some patients are likely to use the private health sector or simply prefer to make use of other hospitals, the sample of biopsies in this study may not fully represent the complete picture of renal disease for patients in the Soweto area. Even though the results from this study have much in common with other studies, generalisation to the broader South African population and renal disease patients in general should be made with caution.

4.10 Conclusion

In terms of the number of biopsy reports reviewed this study is one of the largest renal biopsy studies from South Africa. The sample in this study includes a substantial HIV positive cohort and also covers a longer period than other studies from South Africa.

This study, like others from South Africa and other areas of the world, contributes to our understanding of geographical, gender and age variation as well as changes in patterns of renal disease over time. In particular, this study adds valuable information to the available data regarding the patterns of renal disease

in South Africa and highlights some differences and similarities in patterns in different ethnic groups within South Africa.

The data from this study suggests in a predominantly black population over a 30 year period that

- 1) The most frequent renal pathology was SGN which likely occurred more frequently because of the high frequencies of infectious related glomerular disease – especially renal pathology secondary to HIV - and lupus nephritis- previously thought to be rare in Africa.
- 2) SGN increased over time while PGN declined.
- 3) The most frequent PGNs found were FSGS, MGN and MPGN regardless of HIV status and that IgAN was found infrequently.
- 4) The most frequent causes of NS were FSGS and MGN with FSGS being the most frequent cause in individuals between 12 and 20 years and MGN being the most frequent cause of NS in individuals older than 20years.
- 5) In HIV positive individuals HIVAN was the most frequent cause of NS followed by FSGS.
- 6) HIVAN was associated with a lower CD4 count than other renal pathologies in HIV positive individuals.
- 7) Lupus nephritis was the most frequent SGN.

It is hoped that the data from this, and other studies, will serve as impetus for the development of a central renal biopsy database for South Africa to aid in the most efficient prevention, early diagnosis and treatment of specific renal diseases

and reduce progression to ESRD. Considering the enormous cost associated with the treatment of renal disease, all avenues that could assist in treatment efficiency should be explored.

Genetic profiling of the study population will be of value to determine the actual prevalence of the APOL1 gene in South Africa and the population of Soweto.

Further prospective research regarding patterns of renal disease and studies linking outcomes in this area are also recommended.

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Appendix A – Ethics Approval

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical))

Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

University
of the Witwatersrand,
Johannesburg



12 November 2012

Dr Alda Vermeulen
Department of Internal Medicine
CM Johannesburg Academic Hospital
University

Dear Dr Vermeulen

**RE: Protocol M120874: 'A Review of Patterns of Renal Disease at CH
Baragwanath Hospital from 1982-2011
Request for an extension**

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has reviewed and approved the following amendments on the abovementioned protocol as detailed in your letter dated 30 October 2012:

- Extension of ethics approval to include use of data for a MMed degree

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Secretary
Human Research Ethics Committee (Medical)



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Alda Vermeulen

CLEARANCE CERTIFICATE

M120874

PROJECT

A Review of Patterns of Renal Disease at
Chris Hani Baragwanath Academic Hospital
from 1982-2011

INVESTIGATORS

Dr Alda Vermeulen.

DEPARTMENT

Department of Internal Medicine

DATE CONSIDERED

31/08/2012

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 31/08/2012

CHAIRPERSON 
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES..

Appendix B – Data Collection Form

Data Collection Sheet

Case No	
---------	--

Race	
Black	
Coloured	
Indian	
White	
Other	

Sex	
Female	
Male	

Age	
-----	--

Indications for Biopsy	
Asymptomatic urine abnormalities	
Nephrotic syndrome	
Nephritic syndrome	
Haematuria	
Acute kidney injury	
Chronic kidney disease	
Nephritic/nephrotic syndrome	
Hypertension	

Histo Dx	
Minimal change disease (MCD)	
Membranous nephropathy (MN)	
Focal segmental glomerulosclerosis (FSGS)	
IgA nephropathy (IgAN)	
Mesangioproliferative glomerulonephritis (MsPGN)	
Membranoproliferative glomerulonephritis (MPGN)	
Crescentic glomerulonephritis (Cres GN)	
Proliferative glomerulonephritis (Pro GN)	
Lupus Nephritis class 1	
Lupus Nephritis class 2	
Lupus Nephritis class 3	
Lupus Nephritis class 4	
Lupus Nephritis class 5	
Lupus Nephritis class 6	
HIVAN	
HIVICD	
Post Infect GN	
DM Nephropathy	
AL Amyloid	
AA Amyloid	
Light Chain Dep Disease	
Cryoglobulinaemia	
Immunotactoid GN	
Fibrillary GN	
Benign Hypert Nephrosclerosis	
Malignant Hypertension	

History	Yes	No
DM		
HT		
SLE		
Malignancy		
HAART		

Investigations	Pos	Neg
HIV		
HBV		
HCV		
ANA		
RPR		
ASOT		
ANCA		
Haematuria		

Value	
Protein Creatinine Ratio	
Serum Creatinine	
CD4	