

# CHAPTER 1

## 1.0 INTRODUCTION AND LITERATURE REVIEW

### 1.1 Background

Nephrotic syndrome is a clinical entity that comprises the following features: proteinuria (greater than 3grams in 24 hours), hypoalbuminaemia (serum albumin less than 30g/dl), oedema and hyperlipidaemia.<sup>1</sup> It is essentially due to pathologies that increase the permeability across the glomerular filtration barrier which arises as a result of loss of podocyte ultrastructure. As a result, podocyte foot process eventration and fusion are common features of all disease processes resulting in the nephrotic syndrome. Injury to the podocytes may arise as a result of primary pathologies of the kidneys or as a consequence of a systemic illnesses.<sup>2</sup>

Minimal change nephropathy (MCN) is amongst the commonest cause of nephrotic syndrome worldwide.<sup>3</sup> It accounts for up to 15% of cases of primary nephrotic syndrome in adults<sup>3</sup>; in paediatrics, it accounts for approximately 77% of all cases as described by the International Study of Kidney Diseases in Children.<sup>4</sup> Other causes of primary nephrotic syndrome described include:

- Membranous nephropathy (MN)
- Focal segmental glomerulosclerosis (FSGS)
- Mesangiocapillary glomerulonephritis (MCGN)
- Mesangioproliferative glomerulonephritis (also described as possible variant of MCN)

Minimal change nephropathy is a glomerulopathy in which no significant glomerular changes are found on light microscopy; as a result it is also known as NIL (Nothing-In-Light microscopy) disease. Immunofluorescence studies are also negative but electron microscopy reveals podocytopathy, specifically, fusion of the foot processes.<sup>5</sup>

Minimal change nephropathy can be categorised as primary or secondary. Primary MCN remains largely idiopathic in aetiology with genetic and environmental factors being associated with the disorder. Secondary causes of MCN account for approximately 30% of cases.<sup>6</sup> These causes are diverse and are illustrated in table 1. The table has a comprehensive categorical list but is not completely exhaustive of the examples as they are numerous.

The clinical characteristics of these patients, their disease course and response to treatment have been well described in the paediatric population. In adults, however, fewer series are available and predominantly reflect European and American populations.

**Table 1.** Secondary Causes of Minimal Change Nephropathy

<b>Infections</b>	Bacterial: Syphilis, Tuberculosis, Mycoplasma Viral: HIV, Hepatitis B Parasitic: Schistosomiasis, Helminths, Echinococcus
<b>Drugs</b>	Antimicrobials: rifampicin, ampicilin, cephalosporins Non Steroidal Anti Inflammatory Drugs (NSAIDS) D-Penicillamine Sulfasalazine, Lithium, Interferons Gold
<b>Neoplastic</b>	Hodgkin's Disease Non Hodgkin's Lymphoma Leukemia
<b>Atopy</b>	Pollen House dust Bee stings Dairy products Poison Ivy
<b>MCN superimposed on other renal disease</b>	IgA Nephropathy (IgAN) Systemic Lupus Erythematosus Diabetes Mellitus Autosomal Dominant and Recessive Polycystic Kidney Disease HIV associated nephropathy
<b>Miscellaneous</b>	Sclerosing cholangitis Vigorous exercise Sarcoidosis Thyroid disease; Grave's disease, Thyroiditis Vasculitis Myasthenia gravis (without apparent thymoma) Guillain–Barre syndrome

Adapted from Glassok RJ: Secondary Minimal Change Disease. *Nephrol Dial Transplant*, 2003; 18 Suppl 6:vi52

## 1.2 Epidemiology

Epidemiological data for adult populations suggests that MCN is more common in males and describes a geographical variation with higher prevalence in Asia as compared to North America and Europe.<sup>7</sup> Reviews of the patterns of glomerular diseases from national and regional registries are available in many non-African countries. Only a few such registries are available in Africa, largely due to the limited resources and expertise necessary for performing renal biopsies and histopathological analysis.<sup>8</sup>

Nevertheless, a general trend towards a lower prevalence of MCN has been described in African countries, and particularly, in black Africans (Table 2). In South Africa, Coovadia *et al* (1979) described the occurrence of MCN in 13.5% of black children as compared to 75% of Indian children.<sup>9</sup> Single series studies in Zimbabwe in 1984 and Nigeria in 1990 described incidences of 3% and 6% respectively in children with glomerulopathies.<sup>10,11</sup> A more recent analysis of the patterns of renal disease in South Africa reported a lower incidence of minimal change nephropathy (affecting 3% of African and 8% of Indian children) and also found a prevalence of MCN of 10.7% in black adults presenting with primary glomerular disease<sup>12</sup>. More common in black adult patients was MCGN (35.7%) and membranous nephropathy (21.4%). In Indian patients however, MCN and membranous nephropathy had an equal prevalence of 21.3% and a lower prevalence of 13.3% of MCGN was described.<sup>12</sup> A study undertaken in adult Caucasian patients at a Johannesburg hospital found an incidence of MCN in 13.6% in patients with nephrotic syndrome.<sup>5</sup> A recent review of a single centre renal biopsy database in Cape Town indicated a 6% prevalence of MCN in their adult population, which was reported as

predominantly mixed (coloured) and black.<sup>13</sup> The more common glomerulonephropathies in this study were as follows: MCGN 20.4%, MPGN 19.2%, MN 16.5% and FSGS 10.5%.<sup>13</sup>

**Table 2.** The Trend of Prevalence of Minimal Change Nephropathy in Africa

Study	Adults			Children	
	Black	Indian	White	Black	Indian
<b>Zimbabwe, 1984</b> <i>Seggie J et al</i>				3%	
<b>Nigeria, 1990</b> <i>Abdurrahman MB et al</i>				6%	
<b>South Africa, 1979</b> <i>Coovadia et al</i>				13.5%	75%
<b>South Africa (Johannesburg), 1987</b> <i>Arnold S</i>			13.6%		
<b>South Africa, 1998</b> <i>Naicker S</i>	10.7%	21.3%		3%	8%
<b>South Africa (Cape Town), 2011</b> <i>Okpechi I et al</i>	6%				

Factors such as genetics, socio-economic status, environment and exposure to infections have all been described as probable contributors to the difference in the prevalence of kidney diseases seen in Africa as compared to other continents such as Europe<sup>8</sup>; presumably, these may also play a role in racial discrepancies described above.

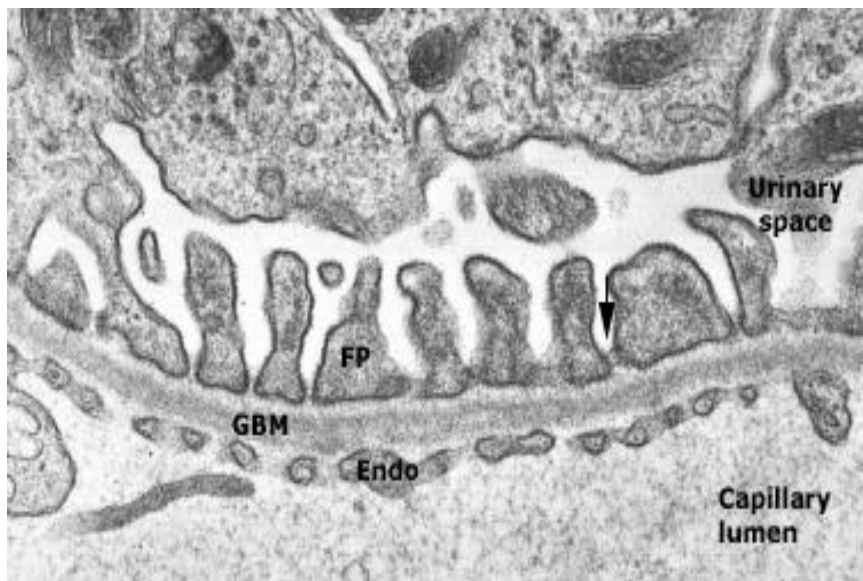
In this regard, MCN has been associated with a number of human leukocyte antigen factors including, DR7, DR8, B12, DQw3.<sup>14</sup> HLADR7 is much more common in white populations than black populations, which may explain discrepancies in MCN prevalence between racial groups.<sup>15</sup> Other studies, however, have failed to show similar associations.<sup>16</sup> A more recent case report described MCN in a patient with limb girdle muscular dystrophy type 2B, which is caused by mutations in dysferlin.<sup>17</sup> Whether this mutation has influence on the incidence of MCN in specific populations has not been determined.

The hygiene hypothesis suggests that good public hygiene and reduced exposure to pathogens in childhood, as assumed to be present in the majority of developed populations, leads to a persistent Th2 phenotype thereby increasing the incidence of glomerulopathies associated with atopic causes such as MCN and IgA nephropathy (IgAN)<sup>8</sup>. African or less developed populations are more exposed to early infections resulting in the development of a Th 1 phenotype and are hence more likely to develop proliferative and crescentic forms of glomerulonephritis. However, this population is also more exposed to infections such as HIV, tuberculosis and schistosomiasis all of which are documented secondary causes of MCN.

### 1.3 Pathogenesis

It is important to understand the structure of a normal glomerulus (Figure 1) in order to fully appreciate the pathogenesis of minimal change nephropathy.

**Figure 1.** Ultrastructure of the Glomerular Capillary Wall



(Endo: Endothelium, GBM: Glomerular Basement Membrane, FP: Foot Process)

Reproduced with permission from: Niaudet P. Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 3rd October 2014) Copyright © 2014 UpToDate, Inc

The glomerular capillary wall comprises three structures: the fenestrated endothelium, the glomerular basement membrane (GBM), and the epithelium with podocyte foot processes with slit diaphragms in between them. These structures create a barrier between the capillary lumen and Bowman's space. Electrophysiological charges and sizes of filtration pores within the above

structures are paramount in maintaining the normal filtration function of the glomerulus. Sialic acid and heparin sulphate contribute to the electronegative charge of the GBM which then repulses negatively charged albumin molecules.<sup>18</sup>

Normal subjects have been described to have sieving coefficients of anionic dextrans radii less than that of neutral dextrans whereas patients with nephrotic syndrome have no difference in sieving coefficients.<sup>19</sup>

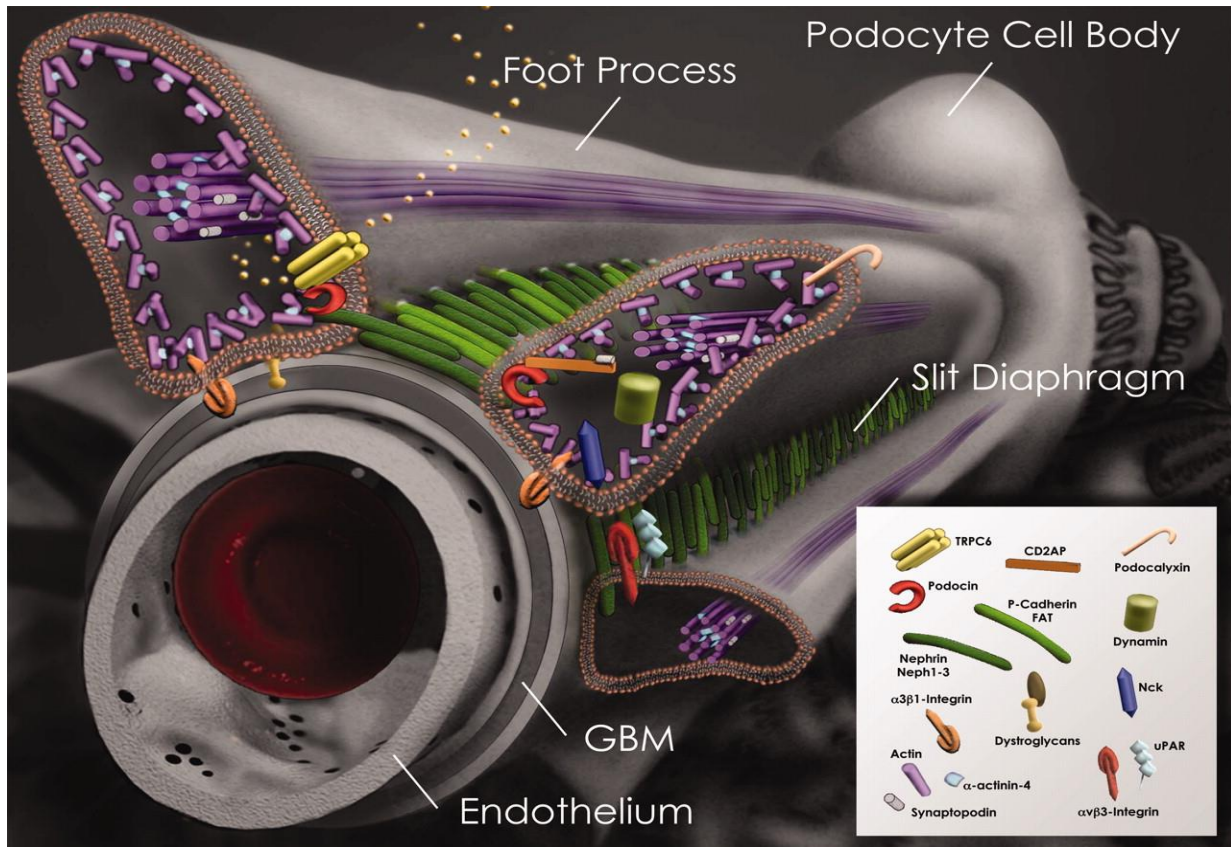
In MCN, data suggests that the electrochemical changes may be involved in initiation of proteinuria. T-cell related mechanisms which are believed to underlie MCN are thought to do so through release of cytokines which cause damage to the glomeruli. It has been hypothesized that a molecule known as glomerular permeability factor (GPF) is produced by undifferentiated T-cells and causes proteinuria by altering the anionic properties of the glomerular basement membrane thereby increasing the permeability of the glomeruli. This is achieved in conjunction with the acute phase reactant, hemopexin,<sup>20</sup> a plasma protein whose synthesis is induced during inflammation.

Data implicates Th2-derived cytokines, particularly interleukin-13 as the postulated glomerular permeability factor<sup>22</sup> (although this still remains to be conclusively determined).

It has also been suggested that B lymphocyte dysfunction may contribute to the production of glomerular permeability factor. Studies showing favourable results of the treatment of MCN with rituximab, a chimeric monoclonal antibody against CD20 subset of B lymphocytes, support this hypothesis.<sup>21</sup>

Glomerular permeability is also greatly affected by the size of the slit diaphragm between podocyte foot processes as it is critical for the size-selective filtration barrier (Figure 2) of the kidney.<sup>23</sup>

**Figure 2.** The Glomerular Filtration Barrier



Reproduced with permission from Moller CC et al. Sensitizing the Slit Diaphragm with TRPC6

Ion Channels: *Journal of the American Society of Nephrology* 2009; 20(5):950-953<sup>24</sup>

As illustrated in Figure 2, critical components of the slit diaphragm include:

- Nephrin: a transmembrane adhesion protein, encoded by NPHS1 responsible for bridging the distance between podocytes. Nephrin deficiency leads to absence of the typical slit diaphragms, podocyte abnormalities and massive proteinuria.<sup>23</sup>
- Podocin: a stomatin family membrane protein, encoded by NPHS 2, interacts with nephrin to form the structural bridge. Genetic mutations of this protein also lead to severe nephrotic syndrome.<sup>25</sup>
- CD2AP : a cytoplasmic multi- adaptor protein also believed to interact with nephrin.<sup>26</sup>

It is important to note that although these mutations are described to cause nephrotic syndrome, they are more closely associated with FSGS.<sup>25</sup>

## **1.4 Diagnosis**

### **1.4.1 Clinical Features**

Patients typically present initially with facial and body swelling accompanied vague symptoms such as fatigue, malaise, headaches, irritability and depression.<sup>3</sup>

Oedema is the most prominent sign and can range from mild to severe. Oedema may progress from facial to anasarca including: scrotal, vulval and sometimes subungual oedema (which is seen as parallel white lines in the fingernail beds). Pleural and pericardial effusions may also occur as a consequence of fluid retention.<sup>27</sup> Blood pressure may be elevated in adult populations but it is said to be normal in most cases.<sup>3</sup>

In MCN, an acute onset, over days to two weeks, is usually described. In contrast, other causes of primary nephrotic syndrome such as FSGS and MN have a more gradual course, developing over weeks to months. This sudden onset in presentation has thus been used as one of the clinical indicators to strengthen the suspicion of MCN as the cause of a specific case of nephrotic syndrome. This sign has been stated to be sensitive but not specific for MCN.<sup>28</sup>

Other findings in the clinical examination and investigation of these patients include: microscopic haematuria, lipiduria, and less commonly acute kidney injury.<sup>28</sup>

The clinical presentation may be associated with complications of nephrotic syndrome such as:

- Increased susceptibility to infections with encapsulated organisms. This occurs due to loss of immunoglobulins due to altered permeability of the glomeruli. It has been postulated that low levels of immunoglobulin G may play a role.
- Increased risk of arterial and venous thrombo-embolism which occurs due to a hypercoagulable state, the mechanism of which still remains to be conclusively determined, but is thought to arise through the loss of anti-clotting factors. Studies have shown occurrence of deep vein and renal vein thrombosis as the most common clinical presentation of this hypercoagulability; however, pulmonary and cerebral vein embolism have also been documented.<sup>29</sup> Arterial thromboses are relatively rare but cases of cerebral, coronary, brachial and femoral artery thromboses have been reported.<sup>30,31</sup>

These complications have been well described both in the paediatric and adult populations.

Waldman *et al* (2007) have studied the frequency of presenting features of adult patients with MCN. The cardinal findings of this study are illustrated in Table 3.<sup>32</sup>

**Table 3.** Relative Frequency of Presenting Clinical Features in Patients with Minimal Change Nephropathy

Clinical Feature	Frequency	Mean
Proteinuria	100%	9.9g/day
Hypoalbuminaemia	100%	2.2g/dl
Hypercholesterolaemia	100%	10.9mmol/l
Haematuria	29%	–
Hypertension	43%	–
Acute Kidney Injury	18%	–

Adapted from Waldman et al: Adult minimal change disease: clinical characteristics, treatment and outcomes. *Clin J Am Soc Nephrol* 2007; 2: 445-453

Clinical features may be age-dependant. It is notable that the cardinal feature of MCN in paediatrics is the abrupt onset of proteinuria progressing to nephrotic syndrome. Haematuria, hypertension and renal dysfunction are unusual in children, but are seen more commonly in adults.<sup>32</sup> Data pertaining to the differences in clinical features due to ethnicity and gender is limited.

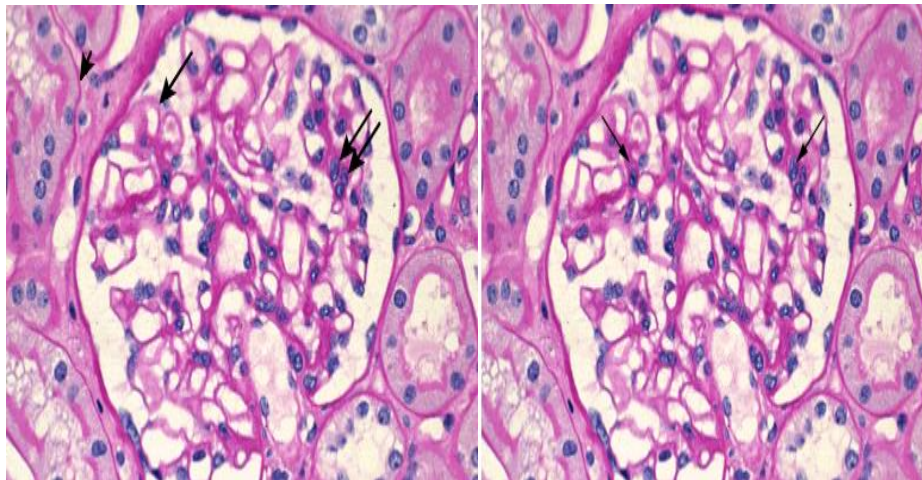
### 1.4.2 Histopathology

The gold standard for diagnosis is renal biopsy. In adults a renal biopsy is indicated in any case of persistent proteinuria where the diagnosis is uncertain. There are several relative and absolute contraindications to renal biopsy which should be ruled out before undertaking the procedure including bleeding diatheses, small kidneys, multiple cysts, hydronephrosis and active renal

infection.<sup>28</sup> In the case of a single kidney, percutaneous biopsy is contraindicated but an open biopsy can still be performed.

A renal biopsy specimen with MCN shows age appropriate tubular atrophy and glomeruli of normal size and cellularity with no segmental abnormalities (Figure 3). On electron microscopy, one can visualise what has been described as the characteristic histologic lesion in MCN, diffuse fusion or effacement of podocytes (Figure 4). The podocyte foot processes are said to retract, widen and shorten leading to their flattened appearance and hence reduction in the number of spaces between them.<sup>33</sup> Adequate treatment and resolution of proteinuria is associated with foot process reversion to normal morphology.

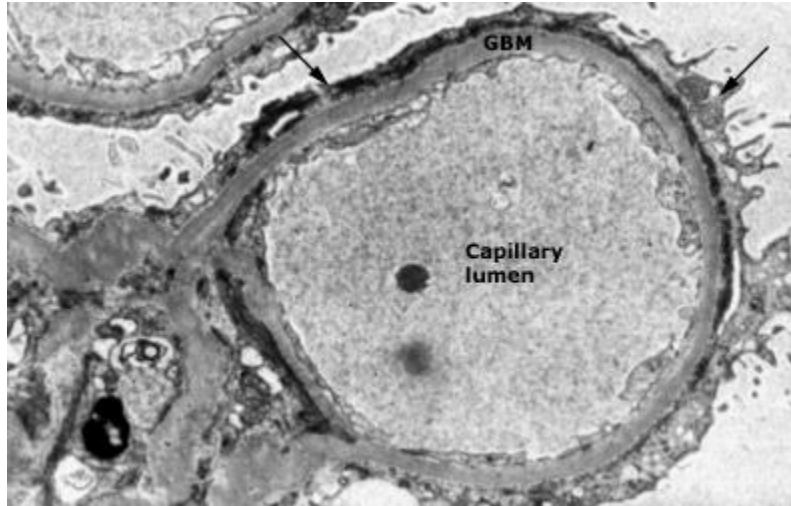
**Figures 3A and 3B.** Light Microscopy of Normal Glomerulus vs Minimal Change Nephropathy



Both figures show normal glomerular structures. **Fig 3A:** Glomerular capillary wall (long arrows), tubular basement membranes (short arrow). **Fig 3B:** Mesangial cells in matrix (arrows)

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**Figure 4.** Electron Microscopy in Minimal Change Nephropathy



Electron micrograph in minimal change disease showing a normal GBM, no immune deposits, and the characteristic widespread fusion of the epithelial cell foot processes (arrows).

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Immunohistological studies can be used to exclude differential diagnoses such as early membranous nephropathy and segmental sclerosing glomerular disorders in which deposits of IgG and complement are seen on the subepithelial aspect of glomerular capillary loops as compared to MCN in which either no or minimal IgM deposits are seen.<sup>20</sup>

## 1.5 Treatment

Available data suggests that MCN is highly responsive to therapeutic regimes consisting of glucocorticoids.<sup>3,34</sup> However, anecdotal evidence would suggest a poorer response in adult and black populations as compared to paediatric and Caucasian populations.

### 1.5.1 Glucocorticoid Sensitive Minimal Change Nephropathy

Prednisone or prednisolone are the mainstay of glucocorticoid therapy which has been described to have a specific effect against proteinuria in addition to their immunosuppressive properties.

This latter effect achieved by decreasing inflammation, reversing the increased capillary permeability and suppressing polymorphonuclear neutrophil (PMN) and lymphocyte activity.<sup>37</sup>

Prednisone is usually given as initial therapy with an average dose of 1mg/kg and a maximum dose of 80mg/day.<sup>35</sup> Variations are seen in many studies as to dosing regimens and the routes of drug administration. Typically, the treatment is continued for a minimum of eight weeks until complete remission is achieved, and then slowly tapered to ensure maintenance of remission, avoidance of adrenal suppression and reduction in the risk of relapse.<sup>34</sup>

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, complete remission of MCN is defined as proteinuria of less than 0.3g per day or urine protein: creatinine ratio (UPCR) less than 30mg per mmol and serum albumin greater than 35g/l.<sup>35</sup> Complete remission in adults is achieved in 51 to 76% within 8 weeks and in up to 96% with 16 weeks of

therapy. In contrast, 93% of children will respond within 8 weeks.<sup>3</sup> Relapses may be more common in adults.<sup>36</sup>

Data suggests that ethnicity may play a role in response to glucocorticoid therapy, with Asian studies reporting more rapid remission rates (80 – 90% by 8 weeks)<sup>34,36</sup> as compared to cohorts with predominantly white populations reporting remission of approximately 75% by 13 weeks.<sup>32</sup> Data detailing glucocorticoid responsiveness in adult Africans as compared to other populations is limited.

### **1.5.2 Glucocorticoid Dependant Minimal Change Nephropathy**

This is diagnosed when patients relapse while on glucocorticoid therapy or when continued glucocorticoid therapy is required to maintain remission. Frequently relapsing MCN, defined as three or more relapses a year, is also considered to be evidence of steroid dependence.<sup>38</sup> Such patients usually require a low maintenance dose of a glucocorticoid and additional immunosuppressant therapy.<sup>38</sup>

### **1.5.3 Glucocorticoid Resistant Minimal Change Nephropathy**

Glucocorticoid resistance has been defined as a lack of significant reduction in proteinuria after 16 weeks of adequate prednisone treatment. This is seen in approximately 5 to 10% of adults with MCN. Postulated reasons for this include inadequate immunosuppressive therapy or possibly incorrect diagnosis, with FSGS being the most likely differential diagnosis.

Glucocorticoid dependent and glucocorticoid resistant MCN requiring the use of additional immunosuppressant therapy are more commonly seen in adults.<sup>39</sup> Additional immunosuppressant therapies may include the following agents:<sup>35</sup>

- Cyclophosphamide
- Calcineurin inhibitors e.g Cyclosporine and Tacrolimus
- Azathioprine and Mycophenolate mofetil (MMF)
- Rituximab

It is important to note that all immunosuppressive therapy has a significant side effect profile and hence the choice of immunosuppressive therapy depends on the patient's tolerance of treatment and minimisation of the side effects encountered.

Non – immunosuppressive therapy is also part of the treatment of patients with MCN. A low sodium diet, fluid restriction and diuresis are advised to assist control of oedema.<sup>40</sup> Hypertension can be treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) as these have an added anti-proteinuric effect. This is mediated by lowering the systemic blood pressure and the intraglomerular pressure which then leads to a reduction in both proteinuria and secondary glomerular injury.<sup>40</sup> Additionally, podocytes are known to express angiotensin II receptors, type 1 (AT1) and type 2 (AT2); angiotensin blockade may therefore be beneficial in the regression of proteinuria and molecular changes in podocytes.<sup>41</sup>

## **1.6 Prognosis**

Minimal change nephropathy has a good prognosis with more than 90% of patients surviving 10 years or more without progression to end stage renal disease<sup>34,36</sup>. End-stage renal disease is rare and has only been reported in steroid-resistant cases.

Focal segmental glomerulosclerosis is often seen on late kidney biopsy in patients with corticosteroid-resistant MCN and in patients who develop progressive renal failure. Whether this represents true progression from MCN to FSGS or sampling error on the initial kidney biopsy due to the focal nature of FSGS, remains uncertain.<sup>36</sup>

## **1.7 Rationale for Study**

Minimal change nephropathy in adult black patients in the local context has not been well studied. This study was therefore conducted to describe the profile of MCN in patients who had renal biopsies at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH), in South Africa over a period of 10 years.

## **1.8 Hypothesis and Aims**

### **1.8.1 Hypothesis**

Minimal change nephropathy is rare in our black adult South African population and is more commonly glucocorticoid resistant.

### **1.8.2 Aims and Objectives**

The primary objective of this study was to determine the profile of patients with MCN.

The secondary objectives were:

- a. The prevalence of MCN in patients who have had renal biopsies at CMJAH and HJH.
- b. The response of MCN to first line treatment with glucocorticoids.
- c. The prevalence of glucocorticoid resistant MCN.
- d. The long term outcomes of the patients with regards to MCN relapse, and progression to renal dysfunction.
- e. The prevalence, presentation and outcomes of black vs. non black patients.

## **CHAPTER 2**

### **2.0 METHODS AND MATERIALS**

#### **2.1 Study Design**

The histopathology records of all patients undergoing native renal biopsy between 2001 and 2010 at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital were surveyed. 1,618 renal biopsies were performed in the ten year period and of these, 55 had a confirmed diagnosis of minimal change nephropathy. The clinical records of these patients were obtained from their respective hospitals and retrospective review of clinical and serological parameters pertaining to MCN was conducted.

Permission to review renal biopsies was obtained from the Department of Anatomical Pathology at the National Histopathology Laboratory Service (NHLS). Review of the records of the patients was permitted by the Chief Executive Officers (CEOs) of CMJAH and HJH as well as the respective Heads of the Nephrology Departments. The protocol for the study was approved by the Postgraduate Committee of the Faculty of Health Sciences and by The Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M120721, Appendix 7.2).

Data pertaining to patient presenting features, response to treatment and outcomes was collected and analysed. As per the data collection sheet (Appendix 7.1), the parameters included:

1. Patient race
2. Patient gender
3. Patient age
4. Patient weight
5. Comorbidities
6. Serum creatinine
7. Serum albumin
8. Serum cholesterol
9. Urine protein : creatinine ratio (UPCR)

Response to therapy was analysed using the following parameters:

10. Duration of therapy required to attain remission
11. Increase in immunosuppression required (e.g. substitution or addition of calcineurin inhibitor) to attain remission.

Remission in this study was defined as per the KDIGO guidelines.<sup>35</sup>

Long term outcomes in this study were assessed through evaluation of the number of relapses, time to relapse and remission profiles.

## **2.2 Selection of patients**

Of the 1,631 renal biopsy histology results reviewed, 47 were recruited into the study. Eight were excluded due to evidence of the presence of co-morbidities that are known secondary causes of MCN namely: HIV (5 patients), systemic lupus erythematosus (SLE) (2) and autoimmune hepatitis (1).

## **2.3 Inclusion Criteria**

Adult patients from CMJAH and HJH with biopsy proven primary MCN were recruited into the study.

## **2.4 Exclusion criteria**

- a. All patients under 18 years of age.
- b. All patients with secondary causes of MCN (Table 1). Secondary MCN as a diagnosis was retrospectively validated using the following criteria:
  - i.) Additional histological patterns present on biopsy consistent with other disease processes (e.g. Diabetic nephropathy, HIV – related renal disease, SLE)
  - ii.) Retrospective case history evidence for the presence of aetiological factors known to be associated with secondary MCN, namely:
    - Diabetes Mellitus
    - Infections: ( HIV, tuberculosis, syphilis)

- Neoplasia (haematogenous and solid organ)
  - Other renal diseases: (SLE, IgAN, autosomal dominant polycystic kidney disease)
  - Atopy
  - Drugs (NSAIDS, lithium, enalapril, tamoxifen, antibiotics, recent immunisation)
- c. All patients with inadequate follow-up (defined as follow-up post diagnosis for less than 6 months). This was to allow adequate period of follow-up for relapse to occur.<sup>32</sup>

## 2.5 Statistical Analysis

Statistical analysis was conducted using STATA software version 13. Normality of distribution of variables was assessed using the Shapiro Wilk W test and the central limit theorem was applied where appropriate. Continuous variables were reported as mean  $\pm$  SD or median and interquartile range as appropriate. Association and significance testing for normally distributed data was carried out using the student t-test; for data that was not normally distributed, the Kruskal Wallis test was used. The chi square test was used to assess significance in categorical binary data. The level of statistical significance was assumed at  $P < 0.05$ . In instances where a difference was noted, further analysis was performed assuming  $P < 0.1$ . Analysis of remission profiles was conducted using the Kaplan-Meier method. Tables, graphs and charts were generated by the programme. In this process, consultation with a statistician was sought.

## **CHAPTER 3**

### **3.0 RESULTS**

#### **3.1 Prevalence**

1,618 renal biopsies had been performed in the ten year period and of these, 55 had a confirmed diagnosis of minimal change nephropathy. 47 were found to have primary MCN and 8 were categorised as secondary MCN.

The prevalence of primary MCN in adults who had renal biopsies at CMJAH and HJH between 2001 and 2010 was thus found to be 2.9%.

1,359 biopsies were performed at CMJAH during this period, and of these 41 (3.0%) had MCN. HJH had 14 MCN cases out of a total of 259 biopsies representing 5.4%.

#### **3.2 Demographic Data**

The demographics and the presenting clinical characteristics of the 47 participants were analysed. These are illustrated in Table 4. The population had almost equal proportions of males (51%) and females (49%). The patients were predominantly of black race (83%) and had a mean age of 31.8±12.1 years.

The patient population had a mean serum creatinine level of  $92.5 \pm 64.3 \mu\text{mol/l}$ , mean albumin level was  $23.4 \pm 11.4 \text{ g/dl}$  with mean cholesterol of  $11.4 \pm 9.1 \text{ mmol/l}$  and a mean protein : creatinine ratio of  $0.69 \pm 0.46 \text{ g/mmol}$ . 18% of patients had creatinine levels above the upper limit of the normal range ( $102 \mu\text{mol/l}$  as per NHLS), while 90% of patients had hypoalbuminaemia (below laboratory normal of  $35 \text{ g/l}$ ) and 89.4% were found to have hypercholesterolaemia (above laboratory normal of  $5 \text{ mmol/l}$ ). Nephrotic range proteinuria (more than  $0.3 \text{ g/mmol}$ ) was present in 81.4% of the population while the rest were subnephrotic.

Hypertension in this study was defined as blood pressure above  $140/90 \text{ mmHg}$ , as per the South African Hypertension Society guidelines<sup>42</sup>, or those on antihypertensive treatment. Hypertension was present in 6.4% of the patients, all of whom were on antihypertensive therapy at presentation.

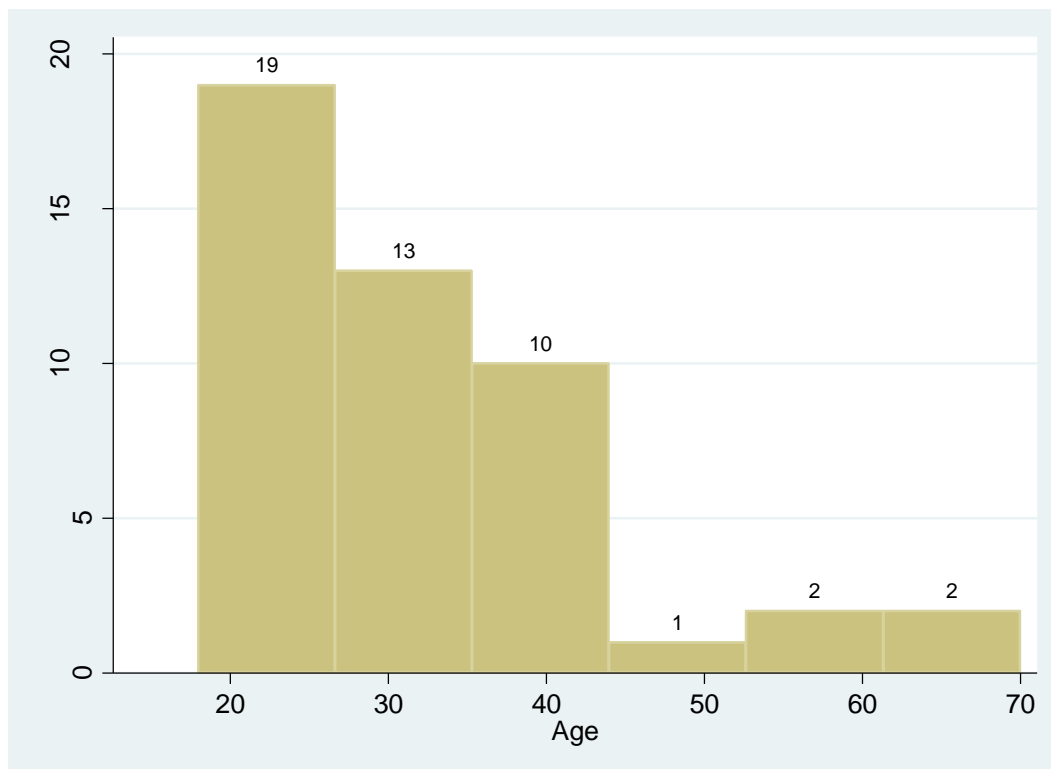
**Table 4.** Baseline Clinical Characteristics of 47 Patients with Minimal Change Nephropathy<sup>a</sup>

Characteristic	Total of Study Population (n=47)
Age (years) (range)	$31.8 \pm 12.1$ (18 -70)
<b>Gender</b>	<b>n (%)</b>
Female	23 (48.9)
Male	24 (51.1)
<b>Ethnicity</b>	<b>n (%)</b>
Black	39 (83)
White	3 (6.4)
Indian	3 (6.4)
Coloured	2 (4.3)
Serum Creatinine ( $\mu\text{mol/l}$ ) <sup>a</sup>	$92.5 \pm 64.3$
Serum Cholesterol ( $\text{mmol/l}$ ) <sup>a</sup>	$11.4 \pm 9.1$
Serum Albumin ( $\text{g/dl}$ ) <sup>b</sup>	21.5 (14.5 – 33)
Urine Protein: Creatinine Ratio ( $\text{g/mmol}$ ) <sup>b</sup>	0.67 (0.40 – 0.95)
Hypertension	3 (6.4)
Renal dysfunction	8 (18.1)

<sup>a</sup> Data are means  $\pm$  SD, <sup>b</sup> Data are median (Inter Quartile Range)

The age distribution of the patients is illustrated in the histogram (Figure 5) below. The distribution is skewed to the right, indicating that the majority of patients are young. 53% of the patients were below the age of 31 and 75% were below 40 years.

**Figure 5.** Age distribution of Patients with Minimal Change Nephropathy



Comparison of the patient profiles was based on the following categories;

- Male vs. Female (Table 5, Figure 6)
- Age <30 vs.  $\geq$ 30 (Table 6, Figure 7)
- Black vs. Non Black (Table 7)

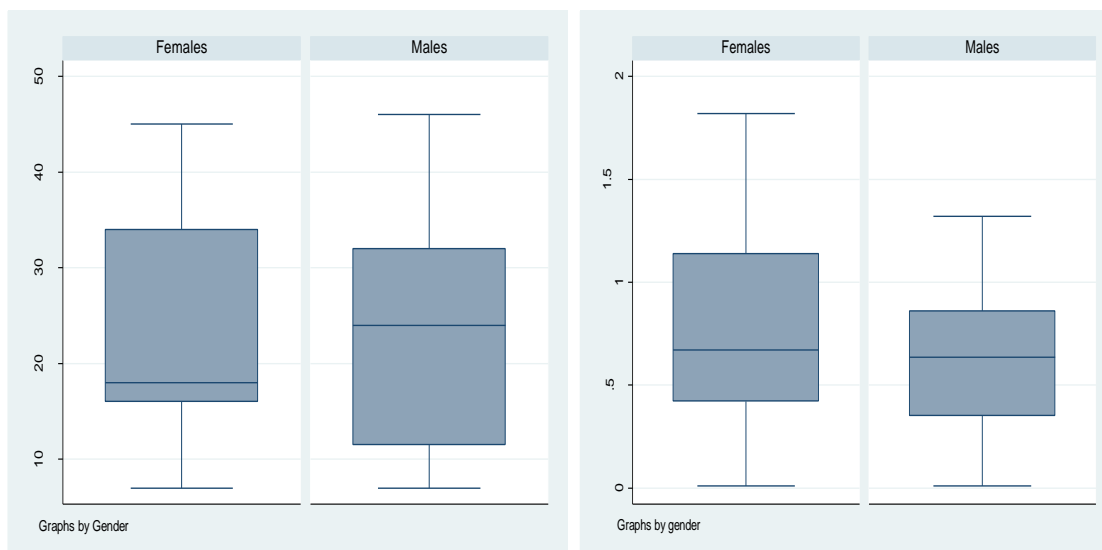
**Table 5.** Comparison of Presenting Characteristics by Gender

	Male n=24	Female n=23	P value
<b>Creatinine<sup>a</sup> (μmol/l)</b>	90.0 ± 34.5	95.4 ± 87	0.2130
<b>Cholesterol<sup>a</sup> (mmol/l)</b>	13.1 ± 11.8	9.6 ± 3.9	0.3805
<b>Albumin<sup>b</sup> (g/dl)</b>	24 (11.5 – 32)	18 (16 – 34)	0.9138
<b>UPCR<sup>b</sup> (g/mmol)</b>	0.64 (0.35 – 0.86)	0.67 (0.42 – 1.14)	0.6270

<sup>a</sup>Data are means ± SD, <sup>b</sup>Data are median (Inter Quartile Range)

The p- values were obtained using the student’s t-test (creatinine, cholesterol) and the Kruskal Wallis test (albumin, UPCR), as appropriate. The median albumin level was higher in males as compared to females. The males however, had a wider interquartile range with a larger proportion of lower values. UPCR levels were generally lower in males as compare to females as shown in table 5 and figure 6. These differences, as well as differences in the other clinical parameters, was not statistically significant the 0.05 level.

**Figure 6.** Comparison of Albumin and UPCR by Gender



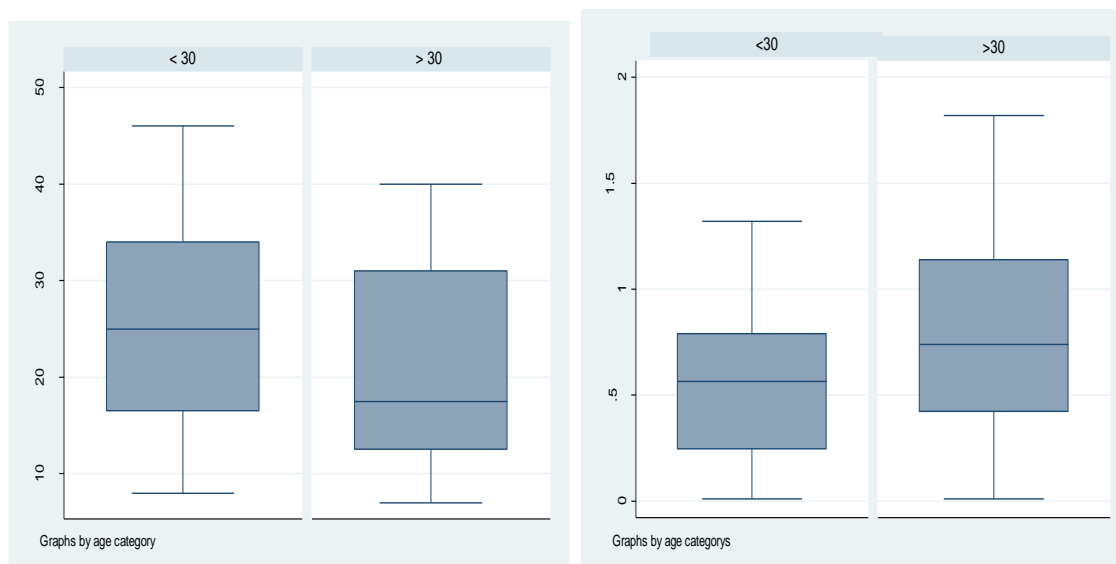
**Table 6.** Comparison of Presenting Characteristics between Age Groups

	Age < 30 n=23	Age ≥ 30 n=24	P value
<b>Creatinine<sup>a</sup> (μmol/l)</b>	89.2 ± 36.8	95.7 ± 82.6	0.9144
<b>Cholesterol<sup>a</sup> (mmol/l)</b>	10.3 ± 4.4	12.5 ± 11.8	0.6065
<b>Albumin<sup>b</sup> (g/dl)</b>	25 (16.5 – 34)	17.5 (12.5 – 31)	0.2499
<b>UPCR<sup>b</sup> (g/mmol)</b>	0.57 (0.25 – 0.79)	0.74 (0.42 – 1.14)	0.2281

<sup>a</sup> Data are means ± SD, <sup>b</sup> Data are median (Inter Quartile Range)

The data in table 6 and figure 7 indicate that the mean/median levels of cholesterol, creatinine and UPCR were lower in the younger age category, while albumin levels were lower in the older age group. The p- values indicate that there was no statistically significant difference in the characteristics between patients in the two age groups, as per the student t-test or Kruskal Wallis test as appropriate.

**Figure 7.** Comparison of Albumin and UPCR levels between Age Groups



**Table 7.** Comparison of Presenting Characteristics between Race Categories

	<b>Black n=39</b>	<b>Non Black n=8</b>	<b>P value</b>
<b>Creatinine<sup>a</sup> (µmol/l)</b>	95.7 ± 69.7	76.1 ± 9.5	0.5514
<b>Cholesterol<sup>a</sup> (mmol/l)</b>	11.9 ± 9.9	9.6 ± 3.5	0.6886
<b>Albumin<sup>b</sup> (g/dl)</b>	22 (16 – 22)	12 (21 – 35)	0.8726
<b>UPCR<sup>b</sup> (g/mmol)</b>	0.67 (0.42 – 0.93)	0.70 (0.34 – 0.98)	0.8028

<sup>a</sup> Data are means ± SD, <sup>b</sup>Data are median (Inter Quartile Range)

There was no significant difference in the characteristics of patients between the race categories.

Further sub analysis between the categories was performed to determine associations. The binary data was described using the Pearson chi square test as follows:

1. an association was found between gender and age such that in younger patients, a predominance of males were diagnosed with MCN as compared to the older age category where a predominance of females was noted (Table 8). This was determined with a p value of 0.057 at the 10% level of significance.
2. there was no apparent association in the prevalence of MCN between age and race with p value 0.477. Given the paucity of non black patients in this population, this outcome may not be truly representative.

**Table 8.** Comparison of Gender and Race vs Age in Patients presenting with Minimal Change Nephropathy

	Age Category	
	<30	≥30
<b>Gender: Male</b>	15	9
<b>Female</b>	8	15
<b>Race: Black</b>	20	19
<b>Non Black</b>	3	5

- no statistical association between the gender and the race of patients with MCN ( $p = 0.947$ ) was found. Almost equal numbers of male and female patients had MCN in the black and non black populations (Table 9).

**Table 9.** Comparison of Race vs Gender in Patients presenting with Minimal Change Nephropathy

Race	Gender	
	Male	Female
<b>Black</b>	20	19
<b>Non Black</b>	4	4

### 3.3 Treatment Outcomes

Of the 47 patients, 28 had records of treatment and outcomes including remission and relapses.

All of the patients received initial therapy with prednisone at a dose of 0.5 – 1mg/kg, the average

dose was 0.8 mg/kg. 57.1 % achieved remission and had no relapses. A total of 12 patients relapsed, of which 58.3% (7) had one relapse and the remaining 41.7% (5) relapsed twice. The risk of relapse depending on presenting variables of patients was analysed and is shown below in Table 10. The p values, as per the t-test or Kruskal Wallis used, suggest that there were no significant differences in the presenting variables between patients who had relapses and those who did not relapse.

**Table 10.** Association between Clinical Characteristics and Relapse

	<b>No Relapse</b>	<b>Relapse</b>	<b>p Value</b>
<b>Creatinine<sup>a</sup> (µmol/l)</b>	89.2 ±36.8	95.7 ±82.6	0.4670
<b>Cholesterol<sup>a</sup> (mmol/l)</b>	12.6 ±11.0	9.36 ±3.2	0.4212
<b>Albumin<sup>b</sup> (mg/dl)</b>	19(11 – 32)	25(17 – 35)	0.1442
<b>UPCR<sup>b</sup> (g/mmol)</b>	0.69(0.27 – 1.04)	0.61(0.42 – 0.76)	0.7756

<sup>a</sup> Data are means ± SD, <sup>b</sup>Data are median (Inter Quartile Range)

The association between age and relapse was also analysed and it was found that 57.1% of patients that relapsed were in the older age category (≥30 years) as compared to 42.9% in the younger category. However, this difference was not statistically significant (p = 0.2949).

Similarly, no significant association was found between race of the patients and the likelihood of relapse (p = 0.241).

The 12 relapsed patients received additional immunosuppressant therapy as follows: cyclosporine (8), cyclophosphamide (2) and tacrolimus (1) and one received another course of

prednisone. One patient received additional therapy with cyclosporine with no significant improvement and achieved remission only after switching to tacrolimus. These 39.2% of patients represent probable steroid dependant or resistant cases in this study. Compliance to treatment is a challenging factor to assess in order to fulfil the definitions of the above entities.

The graph below illustrates time to first relapse (Figure 8). The data indicates that the average time to first relapse was 27.8 months with a standard deviation of 19.4. As shown in the graph, most patients relapsed within 30 months after going into remission. 50% relapsed within 24 months of remission and only 2 patients relapsed after 48 months.

**Figure 8.** Time to First Relapse

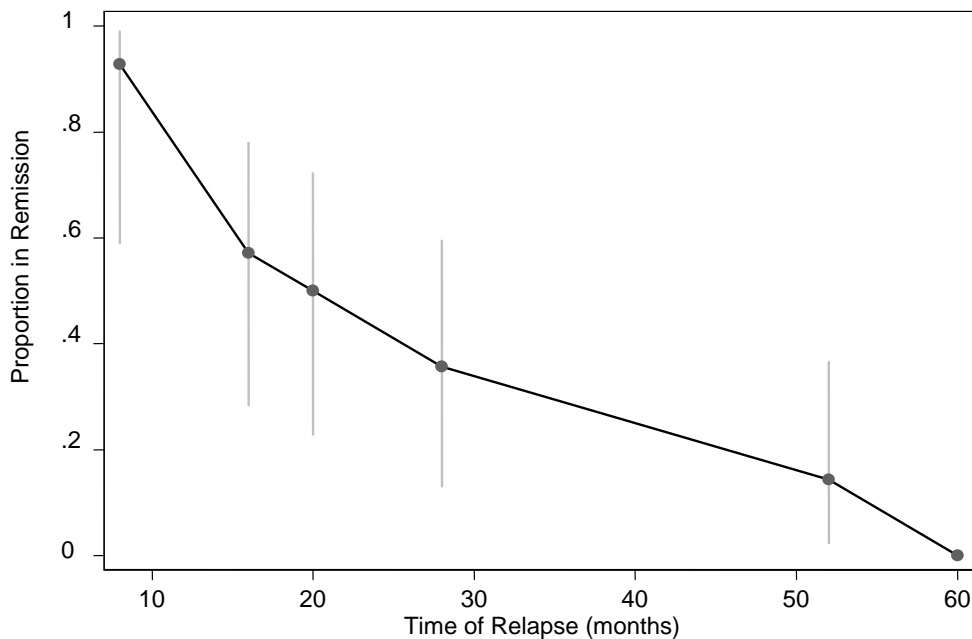


Table 11 below shows the remission periods in intervals and indicates the probability of a patient remaining in remission beyond that interval.

**Table 11.** Remission Intervals

<b>Interval (months)</b>	<b>Total</b>	<b>Relapsed</b>	<b>Probability of remission</b>	<b>Error</b>	<b>[95% Conf. Int.]</b>
<b>4 - 8</b>	12	1	0.9091	0.0867	0.5081 - 0.9867
<b>12 - 16</b>	11	3	0.6364	0.1450	0.2969 - 0.8452
<b>16 - 20</b>	8	1	0.5	0.1336	0.2286 - 0.7221
<b>24 - 28</b>	7	2	0.3571	0.1281	0.1303 - 0.5944
<b>48 - 52</b>	5	3	0.1429	0.0935	0.0232 - 0.3655
<b>56 - 60</b>	2	2	0	.	. .

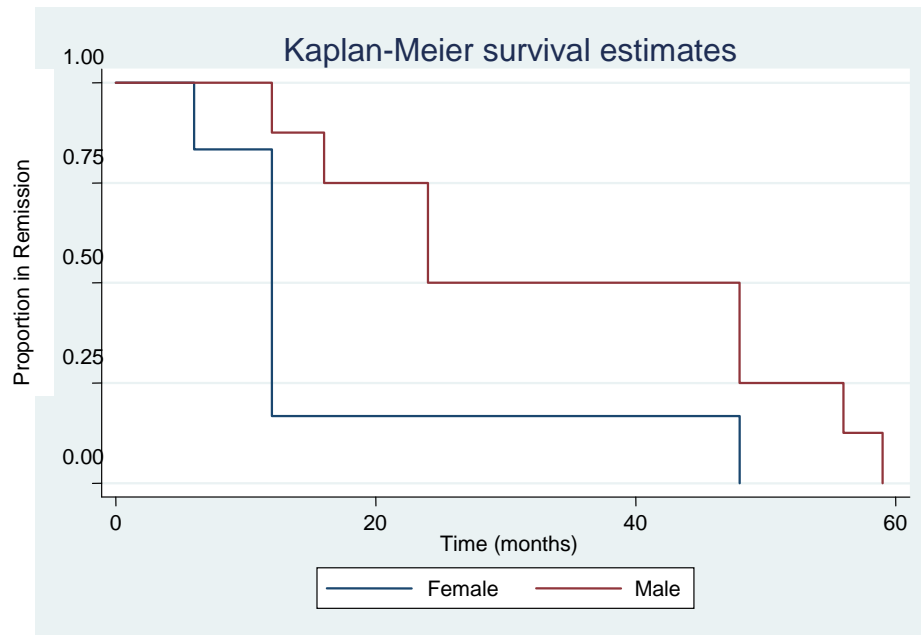
The data shows that the probability of being in remission for over 8 months is 0.90. There is a steady decrease in probability of staying in remission as the time progresses.

### **3.3.1 Comparison of Remission Profiles**

#### **3.3.1.1 Male vs. Female**

It was found that males remained in remission for longer periods compared to females (p value 0.09 significant at 10% level). The data shows that the mean time to relapse for females was 18 ±16.9 months, whereas for the case of male patients, 75% remained in remission beyond 48 months with mean time to relapse of 39.3±17.9 months. Figure 9 below depicts this information.

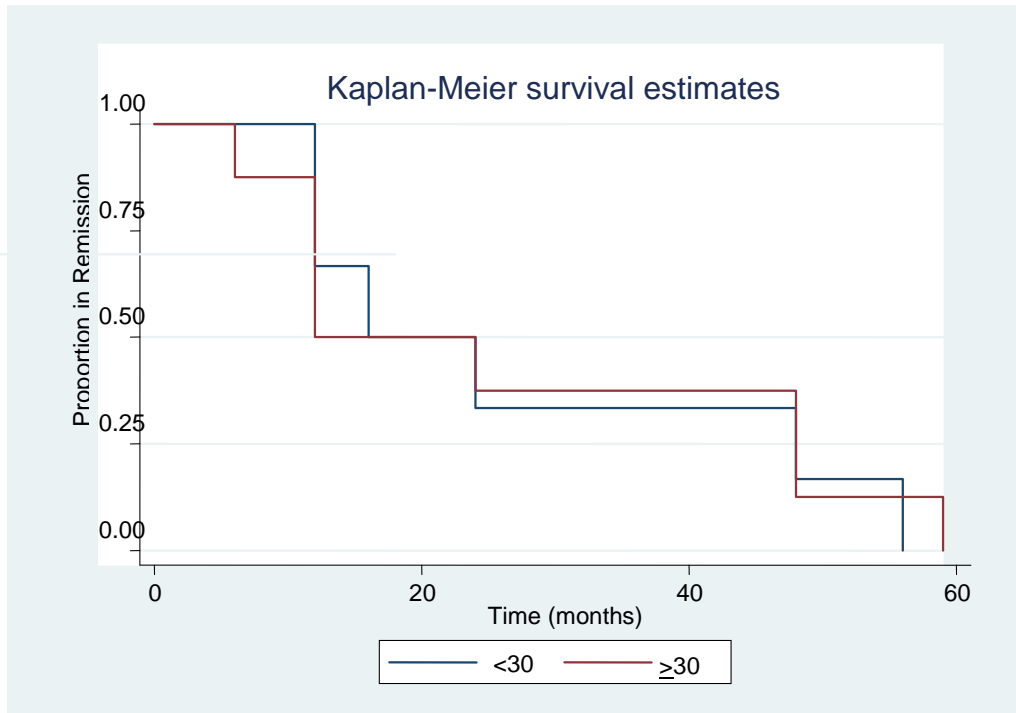
**Figure 9.** Remission Period according to Gender



### 3.3.1.2 Age groups : < 30 vs $\geq$ 30

Analysis demonstrated that the remission profiles for patients aged 30 and above were similar to those who are younger than 30 as shown below (Figure 10):

**Figure 10.** Remission Profiles according to Age Groups



In both categories, 75% of patients remained in remission beyond 12 months and 25% in remission beyond 48 months. However, for patients who are 30 years and older, 50% remained in remission for over 12 months whilst in the younger group patients stayed in remission for longer, with 50% staying for over 16 months.

The remission profile of the patients could not be compared by race (black vs. non black) as only black patients had data for relapse times.

## CHAPTER 4

### 4.0 DISCUSSION

#### 4.1 Epidemiology and Demographics

Minimal change nephropathy has been described as accounting for up to 15% of all causes of nephrotic syndrome in adults.<sup>3</sup> Literature describes higher prevalence in Asia, North America and Europe (7.1 – 15.1%) as compared to Africa.<sup>7-8</sup> In this series, the prevalence was 2.9%, consistent with the lower trend of MCN described in African countries.<sup>8-13</sup> However, biopsies are done on a limited basis (if at all) in many African countries and hence it is difficult to accurately determine the frequency of MCN in Africa.

The fact that this study population was predominantly of black race (83%) supports available data indicating a lower prevalence of MCN in black adults Africans as compared to other racial groups as indicated in table 3. In comparison with a similar series by Arnold , which reported a prevalence of MCN of 13.6% in Caucasian patients at a Johannesburg hospital, it may be concluded that indeed black patients in Johannesburg have a lower prevalence of minimal change nephropathy.<sup>5</sup> Further supporting this finding is data from Naicker (1998), demonstrating a prevalence of MCN in 10.7% of black adults in South Africa<sup>12</sup> and Okpechi *et al* (2011), who found a 6% prevalence in single centre series in Cape Town, where the population is predominantly black and mixed race (coloured).<sup>13</sup>

As previously discussed, genetic factors, socio- economic status and exposure to infection as outlined by the hygiene hypothesis may be implicated to play a role in the aforementioned racial discrepancies.

The age distribution in this study showed that MCN is more prevalent in younger patients. 75% of patients were below the age of 40 years. This is consistent with published data that MCN is seen more frequently in young individuals.<sup>3,7,32</sup>

A male to female ratio of 1.04:1 was found. It would seem, according to this study, therefore, that males and females have an almost equal risk of developing MCN. Data on gender ratios in MCN is varied. Male preponderance, with male to female ratios of 1.8-3.1:1 has been shown in paediatric populations. Interestingly, in this study, a predominance of males was observed amongst younger patients (less than 30 years), as compared to the older category in which more females were diagnosed with the condition. This finding is consistent with the stated paediatric experience. In adults, the studies mostly reflect non black populations and show variable gender preponderance.<sup>4,5,32</sup>

## **4.2 Clinical Characteristics**

The presenting features of the patients were similar to those in other studies, with the vast majority of patients fitting the definition of nephrotic syndrome.

Interestingly, 18% of patients in this study presented with elevated levels of creatinine. Minimal change nephropathy is normally associated with normal creatinine level but studies have shown that patients may present with acute kidney injury.<sup>3</sup> Waldman *et al* (2007) described a similar prevalence of 18% of MCN patients with acute kidney injury in their series of 95 participants.<sup>32</sup> Mak *et al* (1996) reported an even higher prevalence of 55%.<sup>4</sup>

Hypertension is another associated feature seen in adults presenting with MCN. Available data describes it as a presenting feature in up to 47% of cases.<sup>4,32</sup> In this series, the prevalence of hypertension was found to be 6.4%. In general, the incidence and prevalence of essential hypertension indicate that black populations are more likely to develop hypertension.<sup>43</sup> This series however, reflects a lower prevalence. All patients found to have hypertension were already on antihypertensive therapy at diagnosis of MCN. This suggests the possibility of essential hypertension underlying MCN in these patients. The younger age distribution of the study population may have also contributed to the finding of a lower prevalence of hypertension in this study.

In this study, no significant association was found between the presenting clinical characteristics of patients (creatinine, albumin, cholesterol, UPCR) and their race, gender and age group.

## 4.3 Treatment Outcomes

### 4.3.1 Response to initial corticosteroid therapy

In this study, 28 patients had records of treatment and outcomes. Minimal change nephropathy is highly responsive to corticosteroids and hence as initial therapy, all patients received prednisone at an average daily dose of 0.8mg/kg. 57.1% went into remission and had no relapses. This is consistent with data that indicates that complete remission in adults is achieved in 51 to 76% within 8 weeks and in up to 96% with 16 weeks of therapy.<sup>3,34</sup> It was challenging to elucidate the exact time period to remission due to incomplete records, however an average treatment period of 29 weeks was determined from available data.

Adult patients with MCN are believed to require a longer duration of corticosteroid therapy and possibly are more likely to require additional therapy in order to achieve remission.<sup>3</sup> In this study, 12 patients had relapses; 58.3% had a single relapse while 41.7% had two relapses. The average time to relapse was  $27.8 \pm 19.4$  months with the majority of patients (83%) relapsing under 48 months into remission.

Studies appear to show that other race categories have shorter time periods to remission. Asian studies have reported more steroid responsiveness with up to 90% achieving remission by 8 weeks of therapy<sup>34,36</sup> and studies of predominantly white populations report remission rates of 75% by 13 weeks<sup>32</sup> and up to 92% by 21 weeks.<sup>4</sup> The findings in this series, in which patients were mostly of black race, indicate a significantly longer period of treatment needed to achieve remission. Studies have indicated that that no specific presenting clinical feature can

conclusively predict response to corticosteroid therapy.<sup>3</sup> However, Nakamaya M *et al* (2002) suggested that renal dysfunction and extent of proteinuria may negatively influence response to steroid therapy.<sup>36</sup>

No significant associations were found between the likelihood of relapse and variables such as age, gender and race. Moreover, there were no significant differences in the presenting characteristics of the patients who had relapses and those who did not relapse. In this study therefore predicting risk of relapse in an adult patient with MCN has been determined to be difficult. Some studies have also reported no difference in the rate of relapse between age categories.<sup>44</sup> Others, however, have shown more frequent relapses in the less than 40 years age group<sup>32</sup> and in less than 30 years age group.<sup>34,36</sup>

#### **4.3.2 Second line therapy**

Cyclophosphamide is known to induce remission in up to 63%<sup>3</sup> and remains recommended therapeutic modality in the KDIGO clinical practice guidelines.<sup>35</sup> The side effect profile of this agent which includes bone marrow suppression and increased risk of bladder cancer limits its repeated usage. Other agents such as calcineurin inhibitors, azathioprine and MMF have been shown to have better side effect profiles and may be preferred depending on risk and benefit analysis for each patient.<sup>3,32,35</sup> In this study, 39.2% of patients had probable steroid dependence or resistance. Of those patients, 8 were treated with cyclosporine with only 2 receiving

cyclophosphamide and 2 receiving tacrolimus. One patient was switched from cyclosporine to tacrolimus to achieve remission. Available data shows adult steroid resistance to be present in 8% to more than 25% of cases.<sup>4,32</sup>

### **4.3.3 Remission**

The remission profiles of this patient population show that the probability of being in remission for over 8 months is 93%. Males were found to be in remission for longer time period ( $39.3 \pm 17.5$  months) as compared to females who relapsed within a mean time of  $18 \pm 16.9$  months.

Remission profiles according to age categories indicated that 50% of older patients (>30years) stayed in remission for over 12 months whilst in the younger group, patients stayed in remission for longer, with 50% being in remission for over 16 months.

No specific clinical feature was identified to predict remission. Other studies have reported different findings such as Mak *et al* (1996), who reported a positive correlation between remission and albumin level as well as age.<sup>4</sup>

## **CHAPTER 5**

### **5.0 CONCLUSIONS**

The prevalence of MCN in patients at CMJAH and HJH between 2001 – 2010 was 2.9%.

This low prevalence may be a reflection of the ethnicity of the population treated at this institution, which was predominantly of black race.

Younger males and older females may be more likely to present with MCN.

No associated clinical or demographic features can conclusively predict response to corticosteroid therapy.

Males may be more likely to remain in remission for a longer time period compared to females.

## **CHAPTER 6**

### **6.0 LIMITATIONS**

Due to the retrospective nature of this study, incomplete clinical records were encountered limiting patient numbers. This may have had an effect on the analysis of some of the clinical variables.

The sample size was small, as MCN in black adults has a low prevalence. This resulted in some of the data not being normally distributed. Appropriate statistical methods were employed in this case but bias cannot conclusively be disregarded.

A secondary objective proposed in the study protocol was to describe and compare prevalence, presentation and outcomes of black versus non-black patients. Due to the few numbers of non-black patients this objective could not be fulfilled in its entirety. Effort was made to extend the study to Donald Gordon Medical Centre, which is part of the Witwatersrand Academic Complex and caters for a more non-black population but preliminary survey revealed only 2 additional non-black patients for possible inclusion to this study.

## 7.0 APPENDIX

### 7.1 Data collection sheet

<b>Name</b>	
<b>Hospital</b>	
<b>Hospital #</b>	
<b>Age</b>	
<b>Sex (circle)</b>	M            F
<b>Weight (kg)</b>	
<b>Concomitant Hypertension</b> (tick)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Serum Creatinine</b>	
<b>Serum Albumin</b>	
<b>Serum Cholesterol</b>	
<b>Urine P:C ratio</b>	
<b>Corticosteroid given</b>	
<b>Corticosteroid dose / body weight</b>	
<b>Duration of Rx until remission</b>	
<b>Cumulative corticosteroid dose</b>	
<b>Additional immunosuppressant</b>	<input type="checkbox"/> No <input type="checkbox"/> Yes <i>specify</i> _____
<b>Number of relapses</b>	
<b>Time to relapse</b>	
<b>Repeat biopsy</b> (tick)	<input type="checkbox"/> Not done <input type="checkbox"/> Done <i>specify results</i> _____
<b>Time to repeat biopsy</b>	

## 7.2 Ethics Clearance Certificate



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

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**  
R14/49 Dr Mercy J Mkandawire

**CLEARANCE CERTIFICATE**                      **M120721**

**PROJECT**    A Profile of Patients with Minimal Change Nephropathy  
between 2001 and 2010 at the Witwatersrand  
Academic Complex

**INVESTIGATORS**                                      Dr Mercy J Mkandawire

**DEPARTMENT**                                        Department of Internal Medicine  
Charlotte Maxeke Johannesburg Academic Hospital

**DATE CONSIDERED**                                      27/07/2012

**DECISION OF THE COMMITTEE\***                      Approved unconditionally

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

**DATE**    18/11/2013

**CHAIRPERSON** .....   
(Professor PE Cleaton-Jones)

\*Guidelines for written 'informed consent' attached where applicable  
cc: Supervisor :                                      Professor S Naicker

-----  
**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...**

## 7.3 Permissions



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2 October 2014

Mercy J Mkandawire MBBS, FCP  
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Email: [mjmkandawire@gmail.com](mailto:mjmkandawire@gmail.com)

Dear Dr. Mkandawire,

*Figures:* Electron microscopy in minimal change disease (58414)  
Electron micrograph of a normal glomerulus (50018)  
Light microscopy in minimal change disease (71232)  
Normal glomerulus (75094)  
Normal glomerular capillary wall (72505)  
*Topic:* Naudet P. Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children.

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