CLINICO-PATHOLOGICAL CORRELATION AND OUTCOME IN PATIENTS WITH MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS IN CAPE TOWN: A SINGLE CENTRE STUDY

By

ZIBYA BARDAY

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Division of Nephrology and Hypertension

Groote Schuur Hospital

Department of Medicine

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List of Abbreviations

1°	Primary
2°	Secondary
95% CI	95% Confidence Interval
CKD	Chronic Kidney Disease
ESRD	End-Stage Renal Disease
Gd-IgA molecules	Galactose-Deficient IgA Molecules
GSH	Groote Schuur Hospital
HR	Hazard Ratio
IF	Interstitial Fibrosis
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgAN	IgA Nephropathy
IgMN	IgM nephropathy
IDR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease
MesPGN	Mesangioproliferative Glomerulonephritis
Non-IgA MesPGN	Non-IgA Mesangioproliferative Glomerulonephritis
PGN	Primary Glomerulonephritis
UCT	University of Cape Town

ABSTRACT

Background

Glomerulonephritis is a major cause of end-stage kidney disease (ESRD) in Africa. There is scanty data on the clinico-pathological characteristics and outcome of the mesangioproliferative glomerulonephritides in Africa, despite the non-IgA subtype being reported as a common cause of nephrotic syndrome. This study will assess the outcome of patients with biopsy proven mesangioproliferative glomerulonephritis (MesPGN) from a single centre in Cape Town, South Africa.

Methods

The study was designed as 10-year retrospective analysis of patients with biopsy proven MesPGN. The MesPGN patterns were divided into non-IgA MesPGN and IgA nephropathy (IgAN), depending on the predominant type of immune deposit. Univariate cox regression analysis was used to determine factors associated with ESRD.

Results

Data of 109 patients with renal biopsy-proven MesPGN were included for the period between 2005-2014. The mean age at biopsy was 33.8 ±14.9 years, 53.2% were males, and 39.4% were black Africans. Clinically, 58.7% presented with nephrotic syndrome. On histology 79.8% had non-IgA MesPGN, and 20.2% had IgAN. Compared to the non-IgA group, most patients with IgAN were not treated with immunosuppression (72.7% vs. 40.2%; p=0.006). At the last visit, 10.1% had reached ESRD (40.9% vs. 2.3%; p<0.0001) and 30.2% were in complete remission (9.1% vs. 35.7%; p=0.015) for IgAN and non-IgA MesPGN respectively. The 5-year survival for IgAN and non-IgA MesPGN respectively, were: 63.3% vs. 97.6%, log rank p=0.001. Overall, hypertension (p=0.019), not receiving immunosuppression (p=0.046) and having IgAN (p=0.007) were predictors of progression to ESRD.

Conclusion

There is a significantly higher ESRD-free survival of patients with biopsy proven non-IgA MesPGN than IgAN. Whether this is related to the limited use of immunosuppressive therapy in IgAN patients or represents a true nature of the disease requires further research.

Key Words: Mesangial proliferative glomerulonephritis - IgA nephropathy - nephrotic syndrome - end-stage renal disease - South Africa

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

The worldwide incidence and prevalence of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) is steadily rising (1–6). CKD is associated with increased morbidity and mortality, as well as having a strong link as being a cardiovascular risk factor. The burden of CKD and ESRD remains a challenge for the developing and the developed countries.

Glomerulonephritis is common and a significant contributor to CKD, especially in developing countries (7). In Europe, the prevalence of glomerulonephritis is estimated to be 16.3-29.0%, of overall renal biopsies (8). In Africa, some studies report glomerulonephritis to be responsible for up to 49.1% of CKD (9–17). In South Africa, primary glomerulonephritis (PGN) accounts for 34.3% of renal biopsies (7).

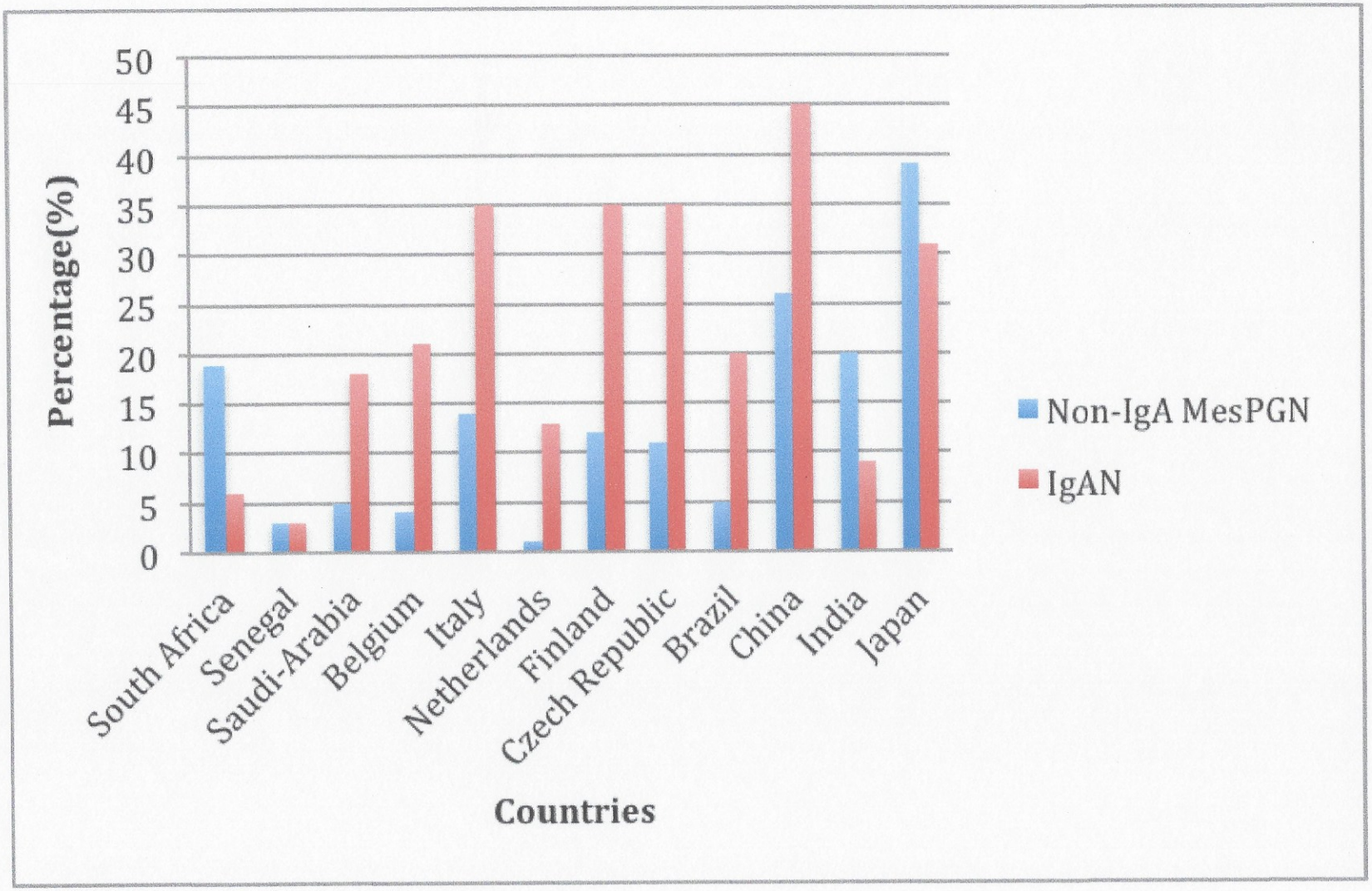
Mesangioproliferative Glomerulonephritis (MesPGN) is a histological pattern that is characterized by mesangial cell proliferation, with or without mesangial matrix expansion. MesPGN can be broadly characterized into two sub-types, non-IgA MesPGN and IgA nephropathy.

In the following sections, the epidemiology, pathogenesis, clinical manifestations, histological features, treatment, prognostic factors and outcomes of MesPGN will be expanded upon.

1.2.Epidemiology of MesPGN

Non-IgA MesPGN is a known common cause of nephrotic syndrome in developing countries, and yet it is rarely described in developed countries. However, IgAN is commonly reported in developed countries and thought to be rare in Africa (18–21).

Worldwide, published data from numerous renal biopsy registries reflect IgAN to be the most common pattern of primary GN (22,23) (Figure 1). A worldwide retrospective analysis of IgAN reveal that males are more likely to be affected than females; and IgAN particularly affects patients during the second and third decade of life (23,24). The global prevalence rate IgAN varies across different ethnicities and geographical regions (Table 1). In Europe, the renal biopsy registries; which include countries such as the United Kingdom, Denmark, Spain, Italy, France, Norway, Czech Republic, Romania and Serbia; IgAN predominates as the most common primary GN and is estimated to be prevalent in 30-40% of all renal biopsies (22,23,25–32). In the United States of America, IgAN is also reported to be the most common primary GN in young Caucasian adults (23). In Asia, renal biopsy registries have had varied results. Countries such as China, Hong Kong and Korea, have an IgAN predominance of 23-45% of renal biopsies performed (23,33–35). However, Japan, India and Pakistan, reflect IgAN not to be a common histological finding (36,37).



Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A Nephropathy.

Figure 1. Prevalence of Mesangioproliferative Glomerulonephritis (non-IgA MesPGN and IgAN) in various countries across the world (1,35,38–47).

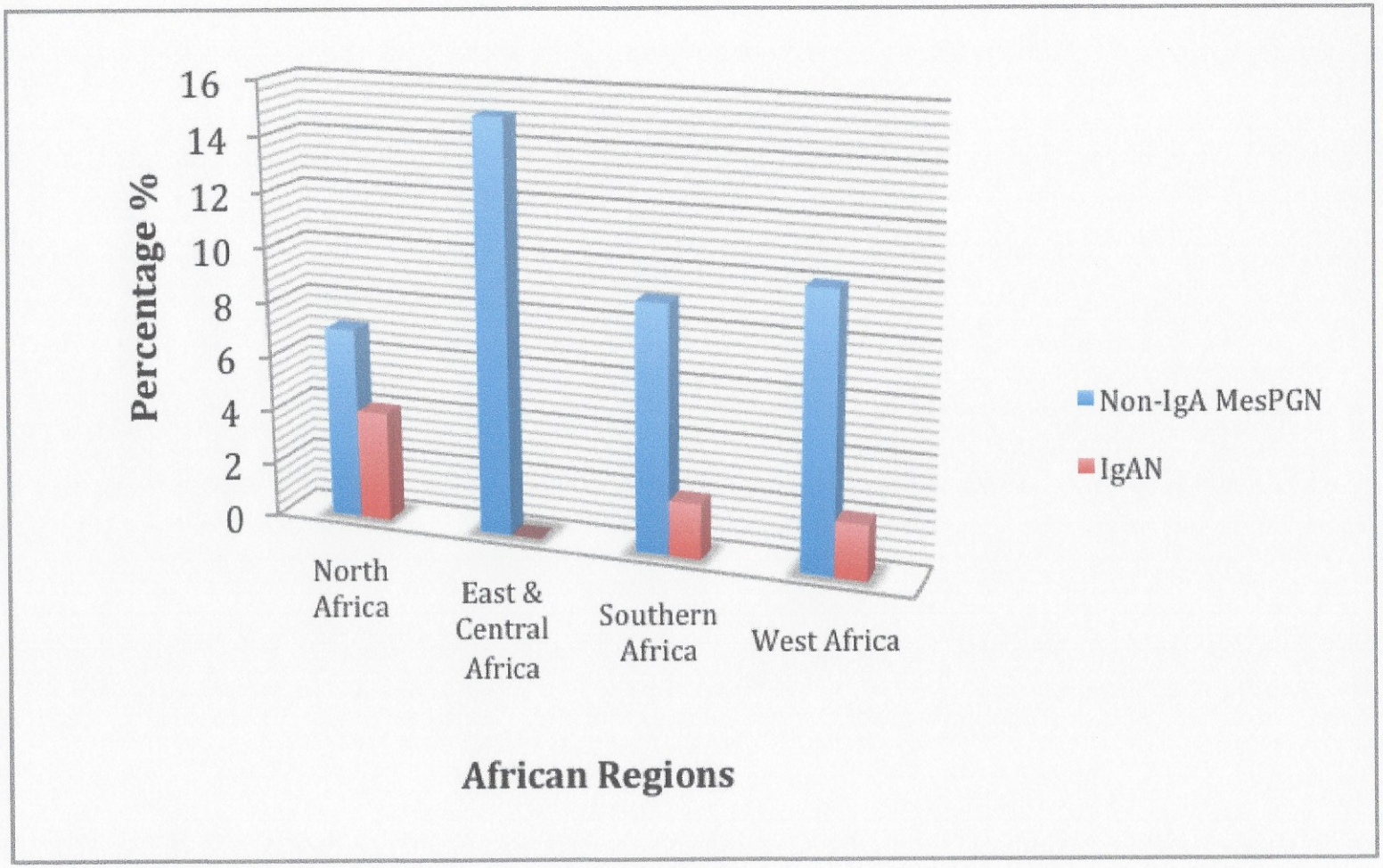
Table 1. Prevalence of Mesangioproliferative Glomerulonephritis (non-IgA MesPGN and IgAN) in studies across the world.

Continent	Country	Author (Reference)	Type of Registry	Duration of Study	Number of Biopsies	1° Non-IgA MesPGN (%)	1° IgAN (%)
Europe	Belgium	Mesquita *et al* (41)	Single Centre	1991-2006	326	4.0	21.2
	Czech Republic	Rychlik *et al* (30)	National	1994-2000	4 004	11.3	34.5
	Czech Republic	Maixnerova *et al* (44)	National	1994-2011	10 472	6.0	37.4
	Denmark	Heaf *et al* (25)	National	1985-1997	2 380	-	10.8
	France	Simon *et al* (27)	Regional	1976-2002	1 742	-	27.3
	Finland	Wirta *et al* (43)	Regional	1980-2000	3310	-	34.9
	Germany (northern)	Braun *et al* (48)	Regional	2001-2008	251	20.9	-
	Italy	Gesualdo *et al* (49)	National	1996-2000	14 607	4.30	16.5
	Macedonia	Polenakovic *et al* (50)	Single Centre	1975-2001	1 304	4.4	11.8
	Netherlands	Van Paassen *et al* (42)	Single Centre	1977-2003	1 348	1.0	12.6
	Romania	Covic *et al* (29)	Regional	1995-2004	635	-	28.9
	Scotland	McQuarrie *et al* (51)	National	2002-2006	2 480	-	14.0-27.0
	Serbia	Naumovic *et al* (31)	Single Centre	1987-2006	1 626	25.1	12.2
	Spain	Rivera *et al* (52)	National	1994-2001	9 378	-	15.2
	United Kingdom	Hanko *et al* (53)	Single Centre	1976-2005	1 844	-	38.8
Australia	Australia	Briganti *et al* (54)	Regional	1995-1997	2 030	-	34.1
North America	United States of America	Swaminathan *et al* (55)	Single Centre	1974-2003	375	-	14
South America	Brazil	Polito *et al* (45)	National	1993-2007	9 062	5.1	20.1
	Uruguay	Mazzuchi *et al* (56)	National	1980-2003	2 058	7.3	12.4
	China	Li *et al* (35)	Single Centre	1979-2002	13 519	25.6	45.2
Asia	Hong Kong	Chan *et al* (57)	Single Centre	1993-1997	1 629	9.5	23.9
	India	Narasimhan *et al* (46)	Single Centre	1986-2002	5 415	20.2	8.6
	Iran	Naini *et al* (58)	Single Centre	1998-2001	407	2.2	13.5
	Japan	Sugiyama *et al* (47)	National	2007-2010	7 034	38.8	31
	Korea	Chang *et al* (34)	Single Centre	1987-2006	1 818	-	28.3
	Saudi-Arabia (west)	Jalalah *et al* (40)	Regional	1989-2007	568	4.7	17.6
	Egypt	Barsoum *et al* (19)	Single Centre	1998-1999	1 234	15.8	NA
Africa	Morocco	Aatif *et al* (59)	Single Centre	200-2007	161	1.1	12.0
	Sudan	Khalifa *et al* (60)	Single Centre	-	89	-	4.7
	South Africa	Okpechi *et al* (38)	Single Centre	2000-2009	1 284	19.2	5.8

1° Non-IgA MesPGN, Primary non-immunoglobulin A mesangioproliferative glomerulonephritis; 1° IgAN, Primary immunoglobulin A nephropathy.

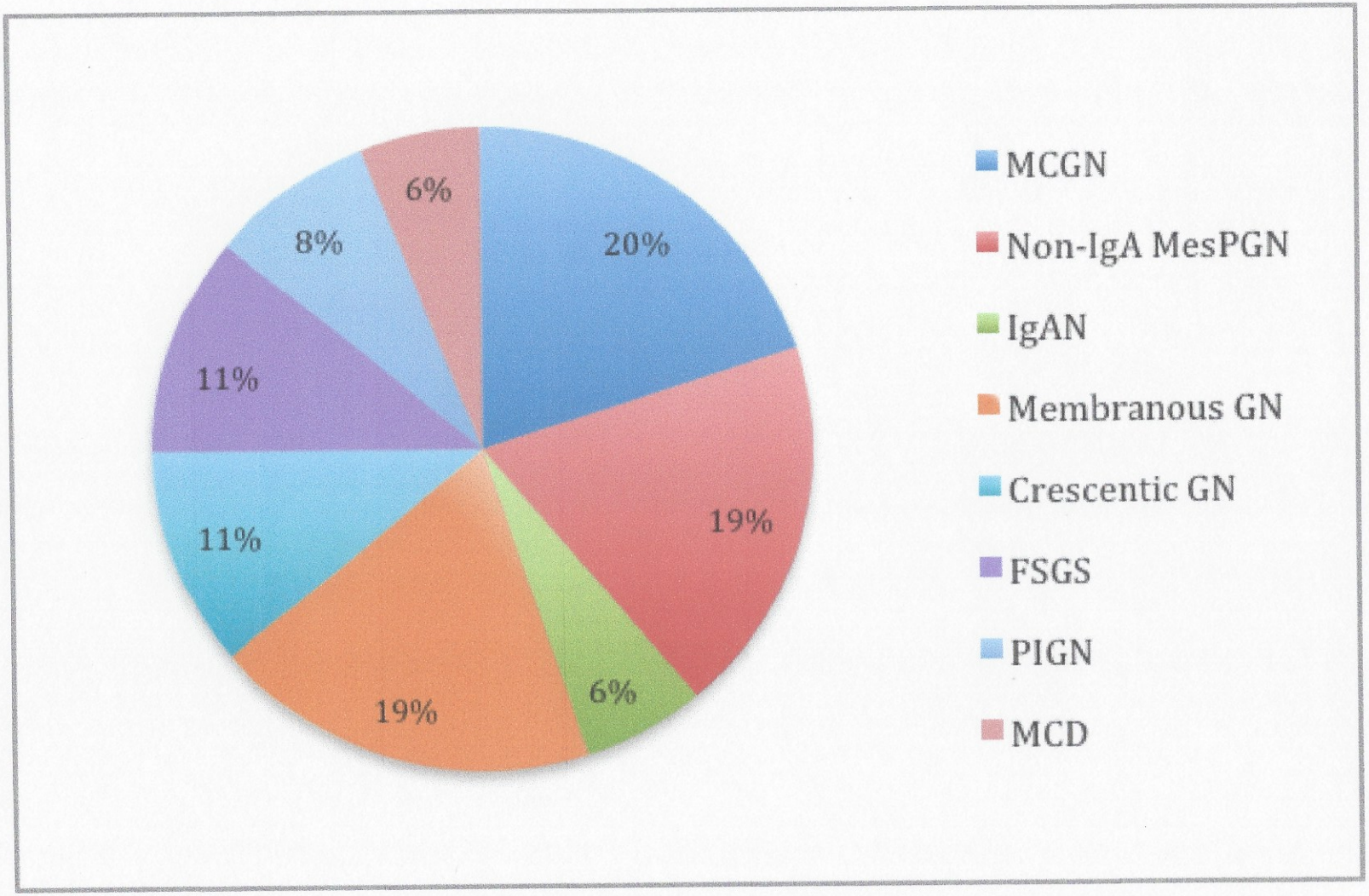
In Africa there is scarce data on the epidemiology of patterns of glomerular disease. The prevalence of non-IgA MesPGN appears to be more commonly found on renal biopsies than IgAN. In a meta-analysis looking at the epidemiology of histologically proven glomerulonephritis in Africa, in different regions across various age groups, overall non-IgA MesPGN was found to be present in 9.2% (95% CI:6.2-12.7; p-heterogeneity <0.0001, difference across age groups: p=0.511) and IgAN in 2.8% (95% CI:1.3-4.9; p-heterogeneity < 0.0001, difference across age groups: p=0.0039) of renal biopsies (18) (Figure 2).

In South Africa, one study from Cape Town evaluated 1284 native renal biopsies and reported non-IgA MesPGN to be the second most common pattern of primary GN (19.2%), with IgAN found in only 5.8% of primary GN biopsied (Figure 3). The same study showed a marked ethnic variation in the distribution of MesPGN subtypes. Non-IgA MesPGN was found in 27.8% Caucasians versus 37.2% other ethnicities (mixed ancestry and black Africans); while IgAN was found only in 4.0% black Africans.



Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy.

Figure 2. Frequencies of Glomerular Diseases in African Regions (18).



MCGN, Mesangiocapillary glomerulonephritis; Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A Nephropathy; Membranous GN, Membranous glomerulonephritis; Crescentic GN, Crescentic glomerulonephritis; FSGS, Focal segmental glomerulonephritis; PIGN, Post-infectious glomerulonephritis; MCD, Minimal change disease.

Figure 3. Distribution of primary glomerular diseases in South Africa (38).

Glomerular diseases present at renal biopsy in Africa tends to be more advanced and severe on presentation; and appears to have a poorer response to treatment when compared to their developed country counterparts (7). Renal biopsy data worldwide is influenced by various factors, including lack of renal biopsy resources and registries, different source populations, time of presentation, different socio-economic status of source populations and the heterogeneity of indications in performing renal biopsies (1). The epidemiology of GN's is strongly influenced by the renal biopsy rate (1). African renal biopsy registries are predominantly single-centered studies, in comparison to developed world countries such as Europe and Australia, where the registries are predominantly multi-centred, regional or national reports.

It is well established that the IgAN prevalence varies among ethnic groups. IgAN has previously been thought to be a rare entity in black Africans (21,61). IgAN accounts for 2.5-5.8% of primary GN on renal biopsies taken in South Africa (21,38,61), Senegal (39) and Sudan (60). In one study conducted by Seedat et al (21), 252 patients with primary glomerular disease were reviewed in KwaZulu-Natal, South Africa; and only 0.8% of patients with IgAN were black. In another single-centre study conducted by Swanepoel et al (61), where 872 renal biopsies in Cape Town, South Africa(61) were analysed; the prevalence of IgAN was 3.8% and none of their cohort study population biopsied were black. IgAN is regarded as uncommon entity in black Africans.

There are a number of theories postulated on why IgAN is rarely seen in black Africans. First, the different prevalence of IgAN observed in different ethnic groups

may reflect genetically determined influences in the pathogenesis of IgAN. Reports of familial IgAN which in vitro have abnormalities in their IgA immune system to some extent, may support the genetic hypothesis (62). IgAN has been linked to certain genes, including chromosome 6q22-23 (IgAN1), 4q26-31 (IGAN2) and 17q12-22 (IGAN3) (63) . Gharavi et al demonstrated that only 60% of IgAN patients could be linked to IGAN1, which suggest that there may be other genes involved which we are not yet aware of. There may be other environmental variables, which could contribute for this variation.

Second, there appears to be a link between the type of glomerular disease and socio-economic status. This expands on the so called "hygiene hypothesis". David Strachan initially postulated in 1889, that early and frequent exposure to infectious antigens, common in the developing world, leads to a Th1 phenotype response. Developed countries have better public hygiene and less risk of infectious antigenic exposure, which leads to a Th2 phenotype response and increases the risk of developing allergic-type reactions. Most proliferative glomerulopathies like MesPGN, MCGN and post-infectious GN are largely driven by Th1 response. These patterns of primary GN are common in developing countries. This correlates to the increased frequency in MCGN seen in South Africa (38), Senegal (64) and Egypt (65,66). IgAN has been shown to have a Th2 dependent mechanism, where Th2 dependent cytokines are mainly produced by circulating T cells in IgAN (67).

Thirdly, different presentations and biopsy practices across the world may influence the prevalence of IgAN in renal biopsy registries. IgAN prevalence in clinical practice may only be the tip of the iceberg compared to the presence of IgAN in the general population. For example, one study which analysed 510 zero-hour allograft biopsies, showed up to 20% of all cases contained glomerular IgA deposits but only 1.6% exhibited mesangioproliferative glomerulonephritis with IgA deposition (68,69). In Africa, the low rate of renal biopsies performed in suspected IgAN may be multi-factorial. This may be due to scarce resources available, limited access to nephrologists, as well as local policies related to performing biopsies in patients with asymptomatic haematuria.

1.3. Pathogenesis of MPGN

There has been progress and extensive research in attempting to achieve a deeper understanding around the pathogenesis of IgAN over the last few decades.

In the advancement in the understanding of the pathophysiology of IgAN, there has been a clear departure from the previous models of an imbalance of IgA production and IgA clearance (70–72). The pathogenesis of IgAN is strongly linked to an autoimmune aetiology. A key pathogenetic role involves underglycated IgA1 molecules, as well as autoantibodies to these IgA glycoforms and IgA receptors. (72). Recent studies reveal that some individuals with high levels of (gal)-deficient IgA (Gd-IgA) are prone to auto-sensitization and the production of anti-Gd-IgA1 antibodies, which form immune complexes contributing to the development of IgAN (73).

The discovery of elevated levels of circulating Gd- IgA in relatives of patients with IgA has led to the development of the two-hit hypothesis. This proposes that the first hit is the presence of abnormal Gd-IgA molecules, which causes asymptomatic or minimal disease. This could explain why 4-16% of patients on autopsy series and kidney donors, were incidentally found to have IgA deposition in the kidneys (68,69). The second hit, is proposed to result in the induction of mesangial oxidative stress with Gd-IgA deposition (74), as well as immune complex formation with circulating IgG or other autoantibodies, which deposit in the glomeruli (75). Higher levels of Gd-IgA and anti-IgA autoantibodies have been associated with more a progressive disease courses, leading to ESRD.

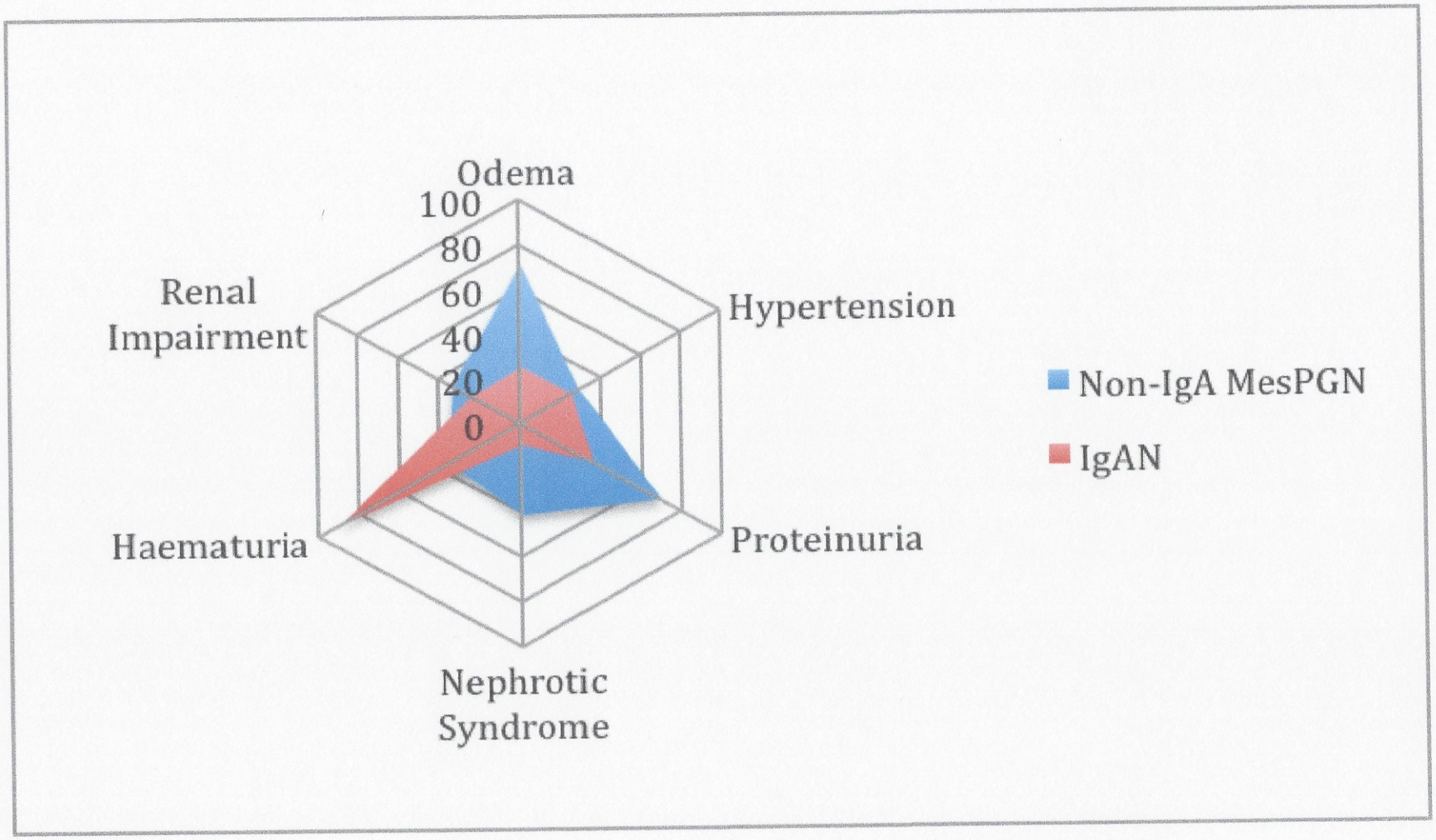
Although the majority of cases with IgAN are sporadic (90%); the genome-wide associated study (GWAS) has discovered genetic loci that explain 40.5% of the cases (76,77). GWAS has also highlighted that the involvement of mucosal defense system and alternative pathways may contribute to the pathogenesis of IgAN.

The pathogenesis of non-IgA MesPGN in comparison to IgAN, remains poorly understood and requires further research.

1.4. Clinical Manifestations of MesPGN

Most patients with IgAN will present initially with macroscopic haematuria, which is usually preceded by an upper respiratory tract or gastrointestinal infection (78). Approximately 40-50 percent patients present with one or recurrent episodes of macroscopic haematuria (79). Some patients may present with asymptomatic

haematuria, with or without mild proteinuria. Less than 10% IgAN will present with acute kidney injury or nephrotic syndrome; with rapidly progressive glomerulonephritis at time of presentation being a rare entity (80,81). The clinical manifestation of non-IgA MesPGN is highly variable, although a number of studies have described a significant number of patients initially presenting with nephrotic syndrome. Other reported clinical presentations include hypertension, haematuria and renal impairment (82,83) (Figure 4).



Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy.

Figure 4. Clinical Presentations of Mesangioproliferative Glomerulonephritis (non-IgA MesPGN and IgAN) (84).

1.5. Histological Features of non-IgA and IgA subtypes of MesPGN

The glomerular mesangium consists of mesangial cells and extracellular matrix (Figure 5). The mesangium is essential in maintaining the structural and functional integrity of the glomerular capillary tuft.

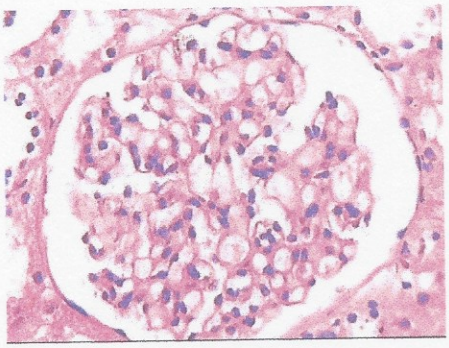


Figure 5: Diagram illustrating the histology of a normal glomerulus (H&E stain). **(Courtesy of Dr F. Botha, NHLS)**

MesPGN is characterized by proliferation of the mesangial cells with increased matrix and/or deposits (immunoglobulins and/or complement) in the mesangial region. Mesangial cell proliferation has an important role in the pathogenesis of progressive glomerular abnormalities, leading to glomerulosclerosis (83). The aetiology of MesPGN may be primary (idiopathic) or secondary resulting from causes such as systemic lupus erythematous, IgM nephropathy, Alport's disease, complement nephropathy, hepatitis, vasculitides or Kimura's disease.

MesPGN can be classified as IgA nephropathy (IgAN) and non-IgA MesPGN (non-IgA MesPGN). IgAN is characterized by the presence of predominantly IgA immunoglobulin deposits in the glomerular mesangium (Figure 6a and Figure 6c).

Non-IgA MesPGN is characterized by mesangial cell proliferation with immune deposits (no IgA immune deposit predominance) or without immune deposits (84) (Figure 6b and Figure 6d). Overall, in all ethnic groups non-IgA MesPGN seems to occur more frequently in the absence of immune deposits rather than in the presence of immune deposits such as IgM, IgG, C3 and C9 (38).

The histology of IgAN can be assessed in terms of the Oxford Classification of IgAN. In 2009, the Renal Pathology Society and International IgA Nephrology Network proposed an international consensus classification for IgAN (85–90) (Table 2). Four histological lesions were found to have predictive prognostic value independent of age and ethnicity. These include mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy or interstitial fibrosis (87,90). There have been a multitude of studies validating the Oxford Classification of IgAN. Several studies confirm the value of tubular atrophy and interstitial fibrosis as predictors of outcome, however the other three parameters have divergent results in studies and remain controversial (88,89,91).

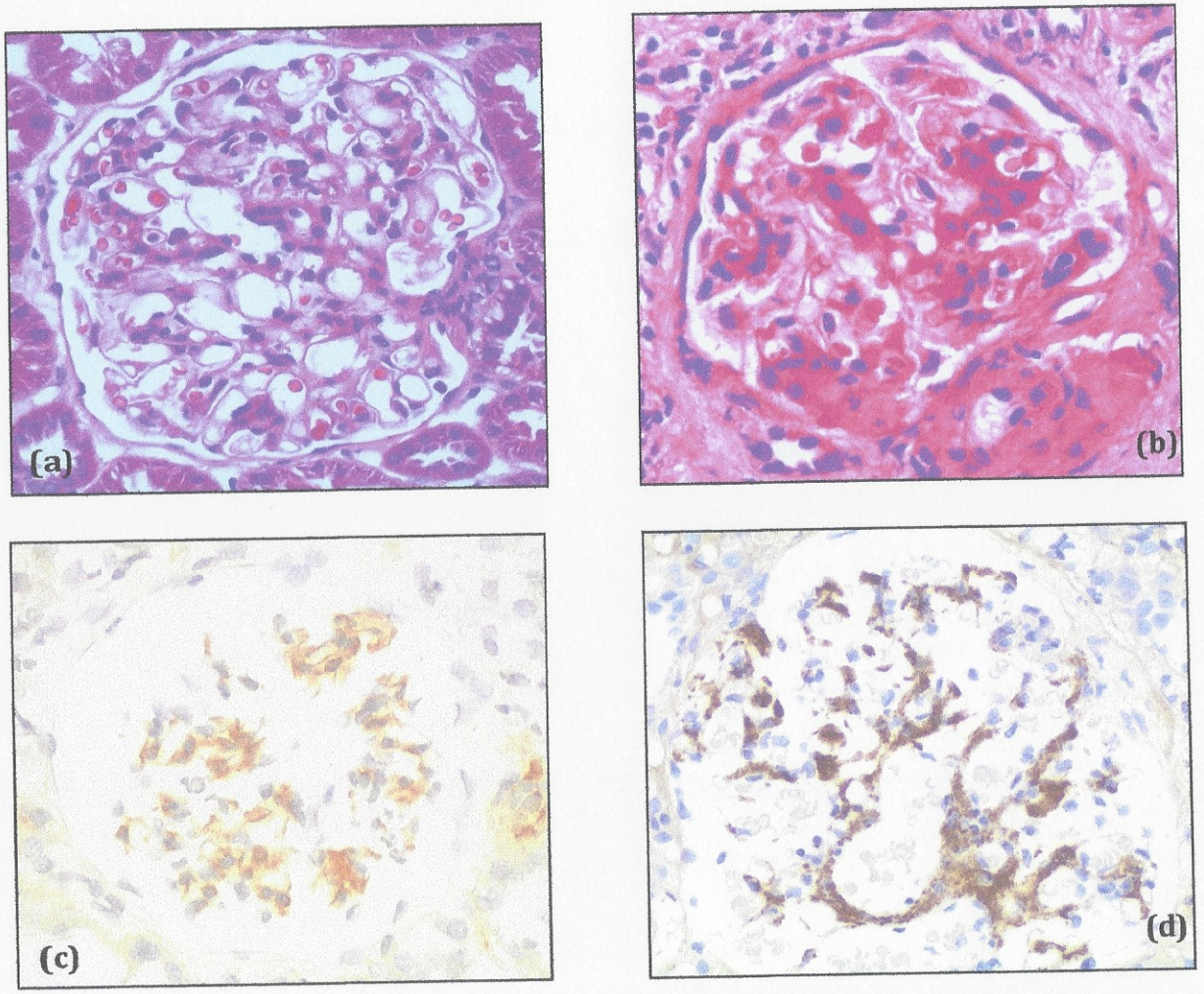


Figure 6: Images of light microscopy (H&E stain) demonstrating glomerular mesangial cell proliferation in IgA nephropathy (a) and non-IgA MesPGN (b). Image of IgAN with immunohistochemical stain positive for IgA deposits (c). Image of non-IgA MesPGN with immunohistochemical stain positive for IgM deposits (d).
(Courtesy of Dr F. Botha, NHLS)

Table 2. Histological Classification of IgA Nephropathy (90).

GRADE	Lee *et al.* 1982 (85)	Haas *et al.* 1997 (86)	Oxford Classification 2009 (87)
I	Mostly normal, slight mesangial thickening with or without hypercellularity.	Minimal histological lesions.	Mesangial hypercellularity ≤50% glomeruli (M0) or >50% glomeruli (M1).
II	Localized mesangial proliferation and sclerosis (rarely small crescents) ≤50% glomeruli.	Focal segmental glomerulosclerosis, with minimal increase in mesangial cellularity, no crescents.	Segmental glomerulosclerosis absent (S0) or present (S1).
III	Diffuse mesangial proliferation and thickening with focal and segmental variation (occasional small crescents), focal interstitial odema and infiltration, rarely tubular atrophy.	Focal (≤50%) proliferative GN (crescents may be present).	Endocapillary hypercellularity absent (E0) or present (E1).
IV	Diffuse mesangial proliferation and sclerosis ≤45% glomeruli, crescents may be present, tubular atrophy, interstitial inflammation.	Diffuse (>50%) proliferative GN (crescents may be present).	Tubular Atrophy / Interstitial fibrosis 0-25% (T0), 26-50% (T1), >50% of cortex (T2).
V	More severe than IV, involves >45% glomeruli.	Advanced chronic GN (≥40% sclerosis, ≥40% tubular atrophy).	

Non-IgA MesPGN is characterised by mesangial proliferation in the presence of non-IgA immune deposits or in the absence of immune deposits. In one study, type of immune deposit predominance (IgM, IgG, C3 or C1q) did not appear to affect progression to ESRD (84). The histology of non-IgA MesPGN is heterogeneous; and as yet there is no formal classification for non-IgA MesPGN as there is for IgAN.

1.6. Treatment of MesPGN

There is no consensus on the most effective treatment for IgAN (92). Non-immunosuppressive therapy is usually given in the treatment of IgAN, while a selective sub-group may benefit from immunosuppressive therapy (93,94).

In IgAN different immunosuppressive regimens have been utilised, consisting of corticosteroids in isolation or in combination with other immunosuppressive agents. Corticosteroids have been recommended in patients who have preserved kidney function and significant proteinuria (protein excretion >1g/day), after a 6 month trial of conservative therapy (95,96). However, key randomised controlled trials, upon which this recommendation was based on, have now been criticized for their inconsistent use of renin-angiotensin system blockade (95,97–99), which may have impacted study outcomes. In the STOP-IgAN study, the addition of immunosuppressive therapy to the intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve outcomes, and there was no change in the rate of eGFR decline (100). There is limited data on the efficacy of the different immunosuppressive agents in patients with IgAN. Corticosteroids in combination with cyclophosphamide or azathioprine may be considered in patients with crescentic IgAN. Two trials evaluated prednisone with either cyclophosphamide followed by azathioprine (101) or with azathioprine alone (102). The patients who received combination therapy had a significantly higher renal survival at 2 years (82 versus 68%) and at 5 years (72 versus 6%), with a significant reduction in urinary protein excretion (101). However, one multi-centered randomised control trial showed that Azathioprine is not as beneficial as compared to corticosteroids alone (102). Mycophenolate Mofetil (MMF) in IgA

nephropathy have been reviewed in four randomised control trials, but the studies reflect mixed results (103–106). Published data on the use of rituximab or corticotropin gel have limited published data and require further studies (93).

Renal transplant is the ideal treatment of choice for patients who have reached ESRD with IgAN, but up to 50% of patients with renal allograft have recurrence of IgAN (107). Living-related transplantation and HLA matching does not confer advantage in graft survival for IgAN patients (107).

Non-immunosuppressive therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), have been shown to slow the progression of IgAN, independent of their effects on blood pressure control (108). The KDIGO guidelines recommend using ACE inhibitors or ARBs to decrease proteinuria and to attain a goal of blood pressure dependent on the level of proteinuria (<125/75mmHg if initial protein excretion >1g/day, <130/80mmHg if initial protein excretion <0.5g/day) (109). Other therapies such as fish oil or tonsillectomy remain controversial (110–112).

Treatment of non-IgAN MesPGN has not been well defined and published data is scarce. Low dose ACE-inhibitors or ARB have a long-term beneficial effect on renal function and proteinuria in patients with non-IgAN MesPGN (113). Cases with isolated haematuria with or without mild proteinuria (<500mg/day) are generally regarded, as benign and no further treatment is necessary other than managing hypertension. For patients with nephrotic syndrome with or without renal impairment, a more aggressive approach is taken. An initial course of immunosuppression with high dose

corticosteroid therapy may be justified in patients with nephrotic range protein, followed by lower doses for additional 3 months. Complete remission may occasionally occur spontaneously. In steroid-dependent or steroid-resistant patients, other steroid-sparing immunosuppressive agents can be utilised e.g. cyclophosphamide, MMF, cyclosporine, azathioprine. ESRD due to non-IgAN MesPGN may benefit from renal transplantation. There are no outcome studies looking at the rate of recurrence of non-IgAN MesPGN in renal allografts.

1.7. Outcome and Prognostic Factors of MesPGN

Characteristics of MesPGN at the time of renal biopsy are of great value and impacts on clinical decision-making, and treatment. Clinical, laboratory and histological variables should be evaluated when assessing the potential renal outcomes of MesPGN.

IgAN is not a benign entity. IgAN is a progressive disease in up to 40% of patients (90,91). The remaining patients have persistent haematuria or proteinuria, and only a small sub-set enter clinical remission. Biopsy proven IgAN at 10 and 20 years, have been reported to progress to ESRD in 15% and 20% respectively (114,115) . The prognosis is highly variable and it is difficult to predict outcomes of individual patients (116).

In IgAN, clinical risk factors that have shown to negatively affect prognosis include age greater than 30 years, male sex, elevated serum creatinine, elevated diastolic blood pressure, proteinuria (>1 g/d 24 h), serum albumin <40 g/l, hypercholestrolaemia and the absence of gross haematuria (84,114,115) (Table 3). In one study, a multi-variant

statistical analysis revealed that high mean arterial pressure and significant proteinuria were independent predictors in IgAN progression towards ESRD (117). Age and mean proteinuria in follow up were also powerful independent prognostic predictors of renal outcome. Histopathological characteristics of IgAN which indicate a poor prognosis include glomerulosclerosis, tubulointerstitial lesions, glomerular crescents, focal or diffuse mesangial proliferation, glomerular tuft adhesions, arteriolar hyalinosis, extension of IgA deposits into the walls of peripheral capillary loops, and glomerular cellular proliferation (114,115).

The clinical and histopathological risk factors described in IgAN may not have the same validity for non-IgAN forms of MesPGN. Moreover, these predictors of outcome in IgAN have not been rigorously assessed, especially in an African setting.

The number of studies published on the course of non-IgAN MesPGN is limited in comparison to IgAN. Non-IgAN MesPGN generally has a better prognosis (118). Studies which previously assessed non-IgAN MesPGN (diagnosis based mainly on light microscopy), report renal survival to be between 80-96% after 5 years and between 64-83% after 10 years (119–122). In non-IgAN MesPGN, clinical factors found to impact renal survival are age, serum creatinine, serum albumin, blood pressure and the presence or absence of proteinuria (119) (Table 3). Histological factors predicting progression to ESRD include focal mesangial sclerosis, focal glomerular crescents or necrosis and an increased interstitial fibrosis score (84).

Table 3. Poor Prognostic Indicators of Mesangioproliferative Glomerulonephritis (Non-IgA MesPGN and IgAN) (119,123).

	Non-IgA MesPGN	IgAN
Clinical	Age >30 years Hypertension	Age >30 years Male sex Hypertension Obesity
Biochemical	Elevated serum creatinine Reduced serum albumin <40g/L Proteinuria	Elevated serum creatinine Reduced serum albumin <40g/L Hypercholestrolaemia Absence gross haematuria Proteinuria >1g/d 24hours
Histological	Glomerulosclerosis Glomerular crescents Mesangial proliferation (focal/diffuse) Glomerular tuft adhesions Glomerular & interstitial cellular proliferation	Glomerulosclerosis Tubulointerstitial lesions Glomerular crescents Focal or diffuse mesangial proliferation Glomerular tuft adhesions Arteriolar hyalinosis Interstitial cellular proliferation

Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy.

1.8. Rationale for Current Study

To the best of our knowledge, there is no published data comparing and describing the outcomes of patients with non-IgA and IgA subtypes of MesPGN in Africa.

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

Clinico-Pathological Correlation and Outcomes in patients with IgA and non-IgA Mesangial Proliferative Glomerulonephritis in Cape Town: A Single Centre Study

Zibya Barday[1], Ikechi G. Okpechi [2,3]

[1] Groote Schuur Hospital and Department of Medicine, University of Cape Town, Cape Town, South Africa

[2] Division of Nephrology and Hypertension, Groote Schuur Hospital and Department of Medicine, University of Cape town, Cape Town, South Africa

[3] Kidney and Hypertension Research Unit, University of Cape Town

Key words:
Mesangial proliferative glomerulonephritis – IgA nephropathy – Nephrotic syndrome – End-stage renal disease – South Africa.

Corresponding Author:
Dr Zibya Barday, Department of Medicine, Groote Schuur Hospital, Observatory 7925, Western Cape, South Africa.

Email: zibs.barday@gmail.com

Tel: +27-21-404 3318, Fax: +27-21-4040 5215

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ABSTRACT

Background

Glomerulonephritis is a major cause of end-stage kidney disease (ESRD) in Africa. There is scanty data on the clinico-pathological characteristics and outcome of the mesangioproliferative glomerulonephritides in Africa, despite the non-IgA subtype being reported as a common cause of nephrotic syndrome. This study will assess the outcome of patients with biopsy proven mesangioproliferative glomerulonephritis (MesPGN) from a single centre in Cape Town, South Africa.

Methods

The study is designed as 10-year retrospective analysis of patients with biopsy proven MesPGN. The MesPGN patterns were divided into non-IgA MesPGN and IgA nephropathy (IgAN), depending on the predominant type of immune deposit. Univariate cox regression analysis was used to determine factors associated with ESRD.

Results

Data of 109 patients with renal biopsy-proven MesPGN were included for the period between 2005-2014. The mean age at biopsy was 33.8 ±14.9 years, 53.2% were males, and 39.4% were black Africans. Clinically, 58.7% presented with nephrotic syndrome. On histology 79.8% had non-IgA MesPGN, and 20.2% had IgAN. Compared to the non-IgA group, most patients with IgAN were not treated with immunosuppression (72.7% vs. 40.2%; p=0.006). At the last visit, 10.1% reached ESRD (40.9% vs. 2.3%; p<0.0001) and 30.2% achieved complete remission (9.1% vs. 35.7%; p=0.015) for IgAN and non-IgA MesPGN respectively. The 5-year renal survival for IgAN and non-IgA MesPGN respectively, were: 63.3% vs. 97.6%, log rank p=0.001. Overall, hypertension (p=0.019), not receiving immunosuppression (p=0.046) and having IgAN (p=0.007) were independent predictors of progression to ESRD.

Conclusion

There is a significantly higher ESRD-free survival of patients with biopsy proven non-IgA MesPGN than IgAN. Whether this is related to the limited use of immunosuppressive therapy in IgAN patients or represents a true nature of the disease still requires further research.

Key Words: Mesangial proliferative glomerulonephritis – IgA nephropathy – Nephrotic syndrome – End-stage renal disease – South Africa.

INTRODUCTION

Glomerulonephritis is one of the leading causes of chronic kidney disease (CKD) and end-stage renal failure (ESRD) in Africa (1,2). The burden of CKD and ESRD remains a global challenge for both developing and developed countries. In Africa, some studies report glomerulonephritis to be responsible for up to 49.1% of ESRD (3,4). In South Africa, primary glomerulonephritis (PGN) accounts for up to 34.3% of renal biopsies (5). Developed countries have a rising incidence of glomerulonephritis and in Europe; glomerulonephritis is estimated to be between 16.3-29.0% of overall renal biopsies (6–8).

Mesangioproliferative Glomerulonephritis (MesPGN) is a common cause of nephrotic syndrome in Africa and is characterized by the proliferation of the mesangial cells with increased matrix and/or deposits (immunoglobulins and/or complement) in the glomerular tuft (9). Mesangial cell proliferation has an important role in the pathogenesis of progressive glomerular abnormalities, leading to glomerulosclerosis (10). MesPGN can be classified as non-IgA mesangioproliferative nephritis (non-IgA MesPGN) and IgA nephropathy (IgAN). Non-IgA MesPGN is characterized by mesangial cell proliferation with either non-IgA immune deposits (IgM, IgG, C3, C9) or the absence of immune deposits. IgAN is characterized by the presence of predominantly IgA immunoglobulin deposits in the glomerular mesangium.

Prognostic outcome studies on non-IgA MesPGN are limited in comparison to IgAN. Non-IgA MesPGN generally tend to have a better prognosis (11,12), however, renal survival in non-IgAN MesPGN is inversely associated with age, serum creatinine, low

serum albumin, high blood pressure and proteinuria, at timing of renal biopsy (11,13). IgAN however, is not a benign entity and tends to be a progressive disease in up to 40% of patients (14–17). IgAN is reported to develop ESRD in approximately 15% and in 20-50% of the cases followed up at 10 years, and at 20 years respectively (14,16). Recent studies indicate that in IgAN, progression of disease is impacted by hypertension, urinary excretion of protein more than 1g/day, and a decreased eGFR of less than 60ml/min/1.73m^2, at time of renal biopsy (18). The aim of this study is to assess the outcome (defined as ESRD at last follow-up visit) of patients with biopsy proven MesPGN (non-IgA and IgA subtypes) from a single centre in Cape Town, South Africa.

METHODS

This study was approved by the Human Research Ethics Committee at the University of Cape Town (HREC REF 338/2015). This study was a retrospective design of patients with biopsy proven MesPGN, identified from Groote Schuur Hospital's renal biopsy database. The case records of all patients between 01 January 2005 to 31 December 2014 were assessed for inclusion into this study. Secondary or other causes of MesPGN (e.g. lupus nephritis, Henoch-Schonlein purpura, chronic liver disease, presence of chronic infections such as hepatitis B, or other active ongoing infections such as syphilis etc.) were excluded from analysis. Renal biopsies of transplant patients were also excluded.

Relevant demographic, clinical, biochemical, histological and treatment data were recorded at baseline, 1 year, 10 years and last follow-up visit. Data collected included age, gender, ethnicity, blood pressure (systolic and diastolic blood pressure), serum

haemoglobin, serum creatinine (including estimated glomerular filtration rate using the MDRD equation (19)), serum albumin and urine protein-to-creatinine ratio (UPCR).

The MesPGN histological diagnosis on renal biopsy was done in accordance with the criteria provided by the WHO monograph of renal disease (20). The characteristic light microscopic findings included mesangial proliferation with expansion of the mesangium with little or no involvement of the capillary lumina. The expanded mesangium required clusters of four or more mononuclear cells per mesangial tuft, with or without an increase in the mesangial matrix. Immunohistochemistry confirmation for the deposition of immune deposits included IgA, IgG, IgM, C3 and C9. Immune deposits could also be visualised with the use of electron microscopy. The presence of deposits was recorded but was not an obligate finding in MesPGN (20).

The following parameters were recorded from the biopsy report in each patient: histological diagnosis (non-IgA MesPGN or IgA nephropathy); the number of glomeruli present, number of sclerosed glomeruli, number of crescents present, type of MesPGN (cellular proliferation or proliferation of mesangial matrix or both), the degree of interstitial fibrosis (none, mild, moderate, or severe), and the type of immune deposits (IgA, IgG, IgM and C3, C9).

The treatment data recorded the use of immunosuppressive therapies (corticosteroids, cyclophosphamide, cyclosporine, azathioprine and mycophenolate mofetil); as well as the utilization of adjuvant therapies including angiotensin-converting enzyme-inhibitors [ACE inhibitors], angiotensin receptor blockers [ARB] or statins.

The main study outcome was the proportion of patients reaching ESRD (eGFR persistently ≤15ml/min/1.73m^2 or the initiation of chronic dialysis).

Definitions

- **Glomerular Filtration Rate**

  The eGFR was calculated using the 4-variable modification of the diet in renal disease (MDRD) equation, in patients who were older than 18 years of age (19).

- **Hypertension**

  Patients were classified as hypertensive if their systolic blood pressure (SBP) was persistently ≥140mmHg and/or diastolic blood pressure (DBP) was ≥ 90 mmHg or if they were on treatment with anti-hypertensive medication (14).

- **Nephrotic Syndrome**

  Nephrotic Syndrome at presentation is defined as clinical entity of proteinuria ≥3.5g/day, serum albumin <30g/L and oedema (21).

- **Remission Status**

  Complete remission (CR), partial remission (PR) or no remission (NR) were used according to the following criteria (10):

  - **Complete Remission:** This was defined as proteinuria of less than 0.2 g/day with stable eGFR if normal at baseline, or increase in eGFR by 25% if abnormal at baseline.

- **Partial Remission:** This was defined as reduction in proteinuria (for proteinuria between 0.2g and 2.9g) and stable eGFR if normal at baseline, or increase in eGFR by 25% if abnormal at baseline.

- **No Remission:** This was defined as persistent proteinuria of 3g/day, or progressive or worsening renal impairment.

Statistical Analysis

Data analysis was performed using SPSS statistical software (SPSS, Chicago, IL, USA). Continuous variables, which are normally distributed, were expressed as mean ± standard deviation (SD) while others were presented at median, interquartile range [IQR]. Comparisons were made using an independent sample student's t-test or Wilcoxon rank-sum test where appropriate. Categorical variables were presented as frequencies and percentages with comparisons made using a Chi-square test or Fisher's exact test. Kaplan-Meier survival analysis was used to assess for overall ESRD-free survival and for survival differences between the 2 groups using the log-rank test. Univariate cox regression analysis was used to determine factors associated with ESRD. Significant p-value was taken as <0.05.

RESULTS

There were 185 patients identified from our renal database with a histological pattern of MesPGN, reported between January 2005 to December 2014. Of these, 76 patients were excluded for various reasons (identified as a secondary diagnosis or not receiving

treatment and follow-up at our centre). Thus, 109 patients were included in this study (79.8% with non-IgA MesPGN and 20.2% with IgAN) (Table 1). The mean age at time of renal biopsy was 33.8 years (range 12-76 years). Nephrotic syndrome was found in 58.7% of all patients, with a greater proportion in the non-IgA MesPGN group (64.4% vs. 36.4%; p-value 0.017). Patients with non-IgA MesPGN had a significantly higher urinary protein excretion (p=0.001), serum cholesterol (p=0.001) and lower serum albumin (p=0.001). There were no significant differences in gender, blood pressure, serum creatinine and estimated GFR between both groups at baseline assessment (Table 1).

On analysis of histological features, patients with IgAN had a significantly higher proportion of sclerosed glomeruli (3.6±5.1 vs. 0.8±2.0; p=0.017). There were no statistical significant differences in the proportion of crescents (p=0.19) and presence of interstitial fibrosis (p=0.18) seen between the two groups. There were significant differences in the patterns of immune deposits seen in our patients; as all patients with IgAN (100%) had IgA deposits in their biopsy (p<0.0001) while 59.8% of patients with non-IgA MesPGN had no deposits (immunoglobulins or complement) on renal biopsy (p<0.0001). The presence of the various immune deposits is summarized in Table 2.

Overall, immunosuppression was used in the treatment of 53.2% of all patients. There were a significantly lower number of immunosuppressive agents utilised in the IgAN group (27.3% vs. 59.8%; p=0.006). In both groups, most patients who received immunosuppression received prednisone. Non-IgA MesPGN were more likely to receive other additional forms of immunosuppression, in contrast to IgAN where only

corticosteroids were utilised (Table 3). Use of renin angiotensin system blockade was similar in both groups.

Remission status was assessed as early remission (at 6months) and late remission (at last visit). At 6 months, complete remission was achieved in 26.4% of non-IgA MesPGN, compared to 14.3% IgAN (p=0.344). At the last visit, 35.7% non-IgA MesPGN were in complete remission versus 9.1% IgAN patients (p=0.015). At the last visit, 2.3% of non-IgA MesPGN vs. 40.9% IgAN (p<0.0001) had established ESRD or were receiving haemodialysis (Table 3). The overall 2-year, 5-year and 10-year ESRD-free survival for both groups was 93.3%, 86.4% and 42.4%, respectively. The 5-year and 10-year ESRD-free survival for non-IgA MesPGN and IgAN was 97.6% vs. 63.3% (log rank p=0.001) and 87.9% vs. 13.2% (log rank p=0.001), respectively (Figure 1A and 1B).

Univariate cox-regression to determine overall predictors of outcome showed that IgAN (p=0.007), hypertension, (p=0.019), interstitial fibrosis in renal biopsy (a surrogate marker of delayed presentation or advanced disease) (p=0.039) and absence of immunosuppressive treatment (p=0.046), were factors that predicted ESRD in all patients (Table 4).

DISCUSSION

Mesangioproliferative glomerulonephritis (MesPGN) is common histological pattern associated with nephrotic syndrome, CKD and ESRD in Africans. Despite this, there is no data on the outcome of patients with biopsy proven MesPGN in Africa. The

importance of this study is highlighted by the main findings, which include (i) higher prevalence of ESRD in patients with IgAN in comparison to those with non-IgA MesPGN; (ii) need to optimize and standardize treatment protocols for all MesPGN patients, given the variation in treatment received by patients; and (iii) the importance of blood pressure control and early disease recognition, given that hypertension and interstitial fibrosis were identified as independent predictors of ESRD.

IgA nephropathy is not a common disease in Africa (20,22). In recognition of IgAN, many clinicians do not offer immunosuppressive treatment, due to the concern of poor response to treatment and the risks associated with immunosuppressive agents. The proportion of patients with IgAN who received immunosuppression in our study was significantly lower than patients with non-IgA MesPGN. Whether the higher proportion of IgAN patients who reach ESRD at last follow up, is related to lack of specific use of immunosuppression in this sub-group or related to the unrelenting nature of the disease, is unknown. Studies that previously show benefit in the use immunosuppression in IgAN have been criticized in terms of their use of RAAS blockade, having either been inconsistent or temporarily halted and then re-initiated at baseline, impacting study outcomes (23–26). In the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) study, the addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve outcomes, as more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decline in the eGFR (27). Other studies have equally show that the addition of immunosuppressive treatment in patients with IgAN provides no additional benefit and may increase

adverse events in such patients (28). Recent studies suggest that the best approach to immunosuppression in IgAN is still unknown. Our study results suggest the need for an approach to treatment of these conditions, based on local experience.

Non-IgA MesPGN is a common condition in Africa (22,29). Although not all patients with non-IgA MesPGN reached early or late, complete or partial remission; it would appear that the response to immunosuppression showed some benefit and slowed down the progression to ESRD. One study from Kenya that assessed the response to steroids and additional immunosuppression in patients with nephrotic syndrome (minimal change disease, MesPGN and FSGS) showed that 36.6% of MesPGN patients reached complete remission following the use of immunosuppressive therapy (29). Although this is similar to our result, there was no separation of MesPGN into IgAN and non-IgAN MesPGN, and the details of the immunosuppressive treatment were not specified in the study. One study from Egypt has suggested that use of cyclosporine was effective in children with idiopathic steroid resistant nephrotic syndrome (MCD, MesPGN and FSGS), as 67% reached complete remission (30). Due to cost and perhaps better response to steroids (with or without azathioprine), there was limited use of cyclosporine in our study. Hence, given the high prevalence of MesPGN in Africans as cause of nephrotic syndrome, our study reinforces the need for a renal biopsy in patients with nephrotic syndrome and early initiation of corticosteroids.

Our study also highlights the importance of blood pressure control in patients with glomerular diseases. Several studies (31–33) have shown that hypertension is a predictor of poor renal outcomes in patients with glomerular diseases. Blood pressure control is protective against the cardiovascular risks of hypertension and delays

progressive loss of GFR. Blood pressure control (including use of RAAS blockade) as a general measure of treatment is one of the factors recommended by KDIGO in the guideline for the treatment of glomerulonephritis. In our study, although most patients in both groups received treatment with ACE-inhibitors or ARBs, BP control may not have been optimal during the period of observation and was noted to be higher in the IgAN group. Our study therefore highlights the importance of BP control in patients with nephrotic syndrome in order to achieve better renal outcomes.

Our study is limited through its retrospective design with a relatively small sample size. The retrospective nature of the study meant that there was no controlled use of immunosuppression in both groups of patients. Ideally, it would be best for patients in both groups to be similarly treated and assessed for response to therapy. Therefore, our study did not truly answer the question of response to therapy in patients with IgAN. However, our study has shown that patients with non-IgA MesPGN have a good response to immunosuppression, with a delay in onset of ESRD. This is encouraging for clinicians who treat patients with nephrotic syndrome in Africa.

CONCLUSION

This study shows that in African patients with nephrotic syndrome there is a significantly higher ESRD-free survival of patients with biopsy proven non-IgA MesPGN than IgAN. Whether this is related to the limited use of immunosuppressive therapy in IgAN patients or represents a true nature of the disease requires further studies.

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TABLES AND FIGURES

Table 1. Comparison of Clinical and Biochemical Features of Non-IgA MesPGN and IgAN.

Factor	All *n* = 109	Non-IgA MesPGN *n* = 87	IgAN *n*=22	P-value
Age (years)	33.8 ± 14.9	34.3 ± 15.7	32.1 ± 11.5	0.54
Gender: Male (%)	53.2	54.0	50.0	0.15
Ethnicity				
Blacks (%)	39.4	43.7	22.7	0.072
Mixed Ancestry (%)	50.5	17	16	
Caucasian (%)	50.5	10	1	
Duration of follow up (months)	29.6 ± 33.4	25.8	43.3	0.21
Hypertension (%)	63.3	31.0	59.1	0.016
Systolic Blood Pressure (mmHg)	133.8 ± 14.9	125.3 ± 15.1	130.1 ± 17.45	0.21
Diastolic Blood Pressure (mmHg)	75.7 ± 11.5	75.7 ± 11.5	75.9 ± 11.61	0.95
Nephrotic Syndrome (%)	58.7	64.4	36.4	0.017
Haematuria	72.5	68.9	95.5	0.011
Serum Creatinine (µmol/L)	156.50	156.3	157.5	0.98
eGFR (mL/min/1.73m^2)	89.2	93.6±55.8	71.7±43.3	0.089
UPCR (g/day)	0.6	0.68	0.25	0.001
Serum Haemoglobin (g/dL)	12.53	12.65	12.07	0.74
Serum Total cholesterol (mg/dL)	9.22	10.14	5.51	0.001
Serum Albumin (g/dL)	28.07	25.9	36.7	0.001

Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy; eGFR, estimate glomerular filtration rate; UPCR, Urine protein: creatinine ratio.

Table 2. Comparison of Histological Features of Non-IgA MesPGN and IgAN.

Factor	All *n* = 109	Non-IgA MesPGN *n* = 87	IgAN *n* = 22	P-value
Glomeruli (n)	16.71	16.5 ± 13.9	17.6 ± 8.5	0.72
Sclerosed glomeruli (%)	1.33	0.8 ± 2.0	3.6 ± 5.1	0.017
Crescents (%)	0.063	0.03 ± 0.24	0.18 ± 0.50	0.19
Interstitial Fibrosis (%)				
None	84.4	83.9	86.4	-
Mild	11.9	13.8	4.5	0.18
Moderate	3.7	2.3	9.1	
Severe	0	0	0	
Type of Immune Deposits (%)				
IgA	21.1	1.1	100	<0.0001
IgM	30.2	31.0	27.3	0.117
IgG	9.2	9.2	9.1	0.988
C3	23.8	14.9	59.1	<0.0001
C9	3.7	2.3	9.1	0.184
No deposits	47.8	59.8	0	<0.0001

Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy; Interstitial Fibrosis Mild, 0.1-0.9%; Interstitial Fibrosis Moderate, 26-50%; Interstitial Fibrosis Severe, more than 50% of renal biopsy; IgA, Immunoglobulin A; IgM, Immunoglobulin M; IgG, Immunoglobulin G; C3, Complement 3; C9, Complement 9.

Table 3. Treatment and Outcome Comparison of Non-IgA MesPGN and IgAN.

Factor	Non-IgA MPGN	IgAN	P-value
Immunosuppression (%)	59.8	27.3	0.006
Prednisone Alone	55.2	72.7	0.128
Prednisone and Cyclophosphamide	6.9	0	0.095
Prednisone and Azathioprine	10.3	0	0.039
Prednisone and Cyclosporine	5.7	0	0.128
RAAS blockade (%)	86.2	81.8	0.862
CR at 6 months (%)	26.4	14.3	0.344
CR / PR at 6 months (%)	69.9	64.3	0.797
CR at last visit (%)	35.7	9.1	0.015
CR / PR at last visit (%)	69.0	54.5	0.201
ESRD at last visit (%)	2.3	40.9	<0.0001

Non-IgA MesPGN, Non-immunoglobulin A mesangioproliferative glomerulonephritis; IgAN, Immunoglobulin A nephropathy; RAAS blockade, Renin-angiotensin-aldosterone blockade; CR, Complete remission; PR, Partial remission; ESRD, End-stage renal disease.

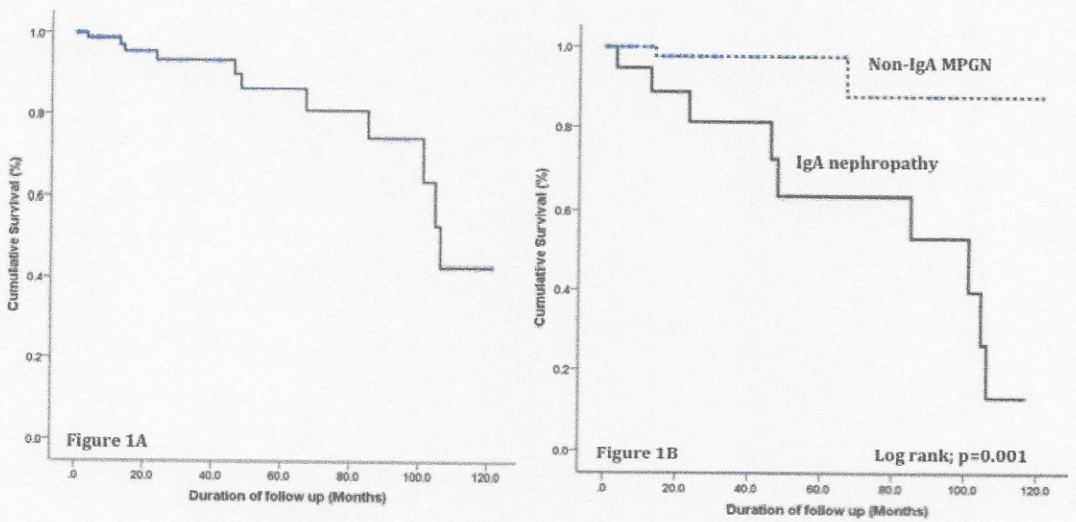
Table 4. Overall Predictors of ESRD.

Factor	OR	95% CI	P-value
IgAN	8.6	1.82-40.68	0.007
Age	1.00	0.95 – 1.06	0.974
Ethnicity (Reference Black Africans)	0.84	0.24 – 2.91	0.779
Gender (Reference Females)	0.55	0.16 – 1.90	0.345
Hypertension	6.3	1.36-29.41	0.019
Nephrotic Syndrome	0.7	0.22-2.40	0.63
Interstitial Fibrosis	3.7	1.07-12.67	0.039
Immunosuppression	0.20	0.04 – 0.97	0.046

OR, Odds ratio; 95% CI, 95 percent confidence interval; IgAN, Immunoglobulin A nephropathy.

LEGEND TO FIGURES

Figure 1: Kaplan-Meier curve for event-free survival from ESRD, for all patients (1A), as well as for non-IgA MesPGN and IgAN (1B).



APPENDICIES

Appendix 1: Clinical Nephrology Instructions to Authors

Clinical Nephrology appears monthly and publishes manuscripts containing original material with emphasis on the following topics: diagnosis, therapy, prophylaxis, immunology and pathophysiology of renal disease, dialysis and renal transplantation.

Preparation of the Manuscript to be submitted in Clinical Nephrology

Word count: maximum 3 600 words, including tables, illustrations and references.

Keywords: maximum 5

The order of the original article should be as follows:

1. The title should be as concise as possible and begin with the main concept in order to facilitate electronic search. The title page should present the institutions and the full postal addresses of all authors. Each author should be correctly linked to the appropriate institution by means of numerical superscripts. The author to whom correspondence should be addressed should also be stated on the title page together with fax, telephone number and e-mail address.

2. The following sequence of arrangement is recommended: abstract, key words, introduction, methods, material, results and discussion, each section being clearly marked.

3. The manuscripts should be typed double-spaced on consecutively numbered pages. The lines should be numbered consecutively.

4. Illustrations, legends, tables, references, abstract [1,400 or less characters with blanks (~ 250 words)] and running title (max. 80 characters) are to be submitted on separate pages but within the same file. The references list, tables and figure legends should be included in the manuscript file, rather than in separate files.

5. The abstract should precisely outline aims, material, method, results and conclusions and be structured accordingly. It should be comprehensible to readers before they read the paper. For the purpose of documentation, indicate 3 to 5 relevant key words that may or may not appear in the title. They should be given below the abstract and separated from each other by a dash (–).

Declaration and Ethics

All authors must enclose a lcovering etter that contain the statement: "The results presented in this paper have not been published previously in whole or part, except in abstract form". All authors are required to give signed consent for publication on a separate sheet together with the covering letter. Possible conflicts of interest following publication must be disclosed.

Appendix 2: Ethics Approval Letter

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

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 May 2015

HREC REF: 338/2015

A/Prof I Okpechi
Nephrology and Hypertension
E13, Renal Unit
NGSH

Dear A/Prof Okpechi

PROJECT TITLE: CLINICO-PATHOLOGICAL CORRELATION AND OUTCOME OF PATIENTS WITH MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS IN CAPE TOWN: A SINGLE CENTRE STUDY (MMed candidate - Dr Z Barday)

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

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th May 2016.

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

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Zibya Barday will also be involved in this study.

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 338/2015