Research Article

Patterns of Glomerular Disease at a Large Urban Public Hospital in South Africa- Impact of HIV Infection

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Abstract:

Introduction

Glomerular disease is an important cause of renal failure. We sought to describe the patterns of glomerular disease in patients undergoing native kidney biopsy at a large urban public hospital in South Africa during the period 2001–2010.

Methods

We retrospectively reviewed all native kidney biopsies undertaken during the study period. We further characterised and compared clinical, laboratory and demographic data between glomerular pathologies.

Results

The majority of patients undergoing biopsy were young (median age 34 years) and of Black African descent (83%). Proteinuria was the most common indication for biopsy. Secondary glomerular disease was more common than primary glomerular disease. HIV-associated glomerular diseases were the most common secondary glomerulopathies Focal segmental glomerulosclerosis (FSGS) was the most frequent primary glomerulopathy. Minimal change nephropathy (MCN) was more frequent in younger patients and membranous nephropathy (MN) more common in older patients. Renal function was poorer in FSGS and membranoproliferative glomerular disease.

Conclusions

HIV is an important contributor to the high rates of secondary glomerular disease. Primary glomerulopathy demonstrates geographic variation in South Africa with FSGS being dominant in Johannesburg. Although clinical parameters may suggest underlying glomerulopathy, an accurate diagnosis to facilitate directed treatment and prevent progression to renal failure requires a renal biopsy.

Keywords: Glomerular disease, glomerulonephritis, kidney dysfunction, HIV

INTRODUCTION

Primary glomerulopathy appears to show temporal and regional variation in the frequency of presentation.(1) Whilst this may partially be explained by differences in locally accepted indications for biopsy, true geographic variation may arise from differences in the local environment, socioeconomic status of the population, and prevalence of certain infections.(2) It has been suggested that primary glomerular disease is more prevalent in developing countries, where progression to kidney failure is more common. Available literature from South Africa suggests that glomerular disease is more frequent in Black African patients, reflecting the interplay of socio-economic factors superimposed on genetic susceptibility.(3,4)

The South African Dialysis and Transplant Registry in 1994 reported glomerular disease to be the cause of 52.1% of cases of kidney failure.(4) An older study, reported 40 years ago from the largest public hospital in South Africa, Chris Hani Baragwanath Hospital (CHBAH), found that chronic glomerulonephritis contributed to 40% of cases of kidney failure.(5) A report from Bloemfontein found nephrotic syndrome to be the most common indication for biopsy, with focal segmental glomerulosclerosis (FSGS) being the most common primary glomerular disease followed by membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN) and minimal change disease (MCD).(6) In contrast, researchers in Cape Town found MPGN to be the most frequent histological finding (20.4% of biopsies)

followed by mesangioproliferative glomerulonephritis (19.2%), MN (18.5%), crescentic and necrotizing glomerulonephritis (11.4%), with FSGS (10.5%) and MCD (6.0%) being comparatively uncommon.(7)

A retrospective review of native biopsies conducted at CHBAH also found FSGS to be the most frequent pathology.(8,9) In a recent report from another public health facility in Johannesburg (Helen Joseph Hospital), found high rates of secondary glomerular disease, with HIV-associated kidney diseases accounting for 25.8% of cases, followed by lupus nephritis in 20.9% of cases.(10) Amongst primary glomerular diseases, FSGS was the most common lesion in this cohort.(10)

In comparison, biopsy findings at the second largest public hospital, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), in Johannesburg has not been previously reported. The current study was thus undertaken to characterize glomerular disease patterns at this institution in order to broaden the knowledge of this condition in South Africa.

METHODS

A retrospective review of all adult patients undergoing kidney biopsy at CMJAH, during the period January 2001 to December 2010 was undertaken. Biopsies undertaken in transplant recipients and those performed on paediatric patients were excluded, as were all cases with insufficient data available to permit meaningful analysis. After exclusion, data from 372 biopsies out of 1495 biopsies performed during the study period were identified for inclusion in this study.

Data pertaining to patient demographics, indication for biopsy as per contemporaneous clinical record, peri-biopsy laboratory data, and histological diagnosis, was extracted anonymously and stored in a secured Excel database (Microsoft Corporation) prior to export to Statistica version 14.0 (TIBCO Software Inc) for analysis. Histological diagnoses were subcategorised as primary or secondary. Secondary glomerular disease was defined by the presence of systemic disease processes (diabetes mellitus, hypertension, systemic lupus erythematosus, Hepatitis B or C and HIV infection) detected either on biopsy or indicated by contemporaneous laboratory or clinical parameters. In this definition, auto-immune disorders such as the ANCA vasculitides and Goodpasture's disease and syndrome were considered as secondary glomerular diseases. Patient demographic parameters, indication for biopsy, and laboratory parameters were compared between primary and secondary glomerular disease categories and histological diagnoses using Chi-square testing or the ANOVA or Friedman test, as appropriate.

Permission to undertake this study was granted by the Human Research Ethics Committee of the University of the Witwatersrand.

RESULTS

Baseline characteristics of the sample cohort are shown in Table 1. Included patients were young (median age 34 years, interquartile range 27–44 years), predominantly of

Table 1: Baseline characteristics of the sample cohort (n = 372)

	n (%)	Median [interquartile range]
Sex		
Male	193 (51.9%)	
Female	179 (48.1%)	
Age (years)		34 [27–44]
Ethnicity		
Black African	309 (83.1%)	
White	41 (11.0%)	
Indian	17 (4.6%)	
Mixed ethnicity	3 (0.8%)	
Asian	2 (0.5%)	
Indication to biopsy		
Nephrotic range proteinuria	223 (59.9%)	
Unexplained renal dysfunction	106 (28.5%)	
Subnephrotic proteinuria	36 (9.7%)	
Nephritic syndrome	4 (1.1%)	
Isolated haematuria	3 (0.8%)	
Laboratory parameters		
Serum creatinine (μmol/L)	371 (99.8%)	162 [86–472]
Serum cholesterol (mmol/L)	243 (65.3%)	5.3 [4.2–7.9]
Urine protein: creatinine ratio (g/mmol)	369 (99.2%)	0.50 [0.25–0.95]
Urine white cell count (cells/mm^3)	249 (66.9%)	22000 [8000–72000]

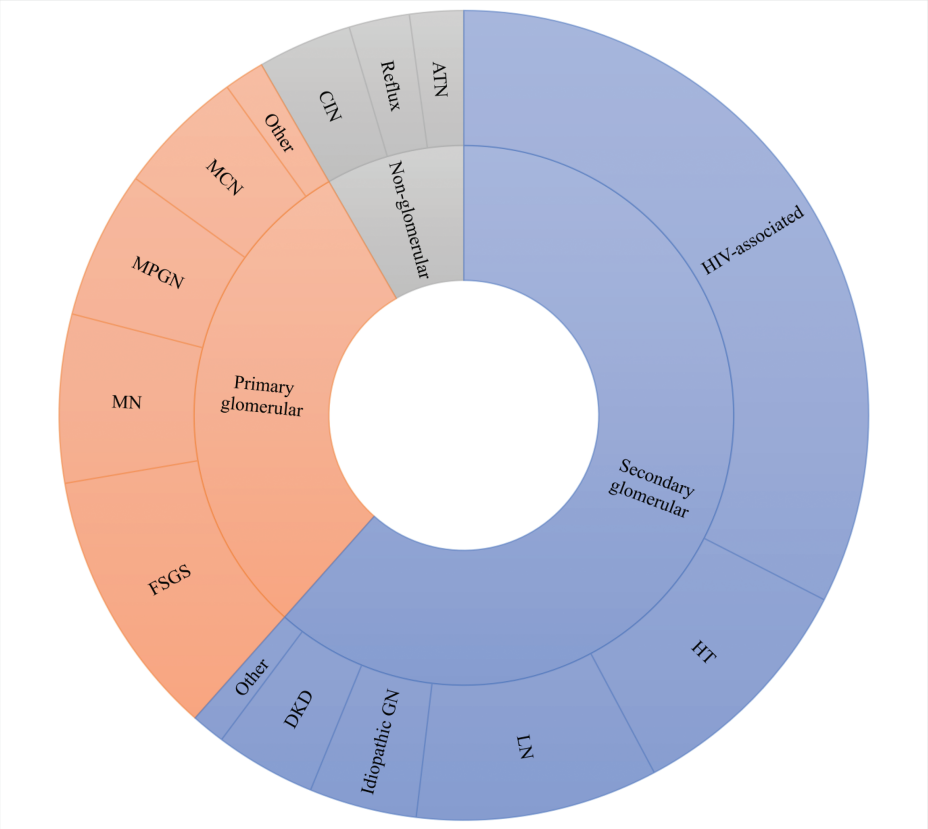

Figure 1: Distribution of biopsy diagnoses

Black African ethnicity (83.1%), with a slight male preponderance (51.9%). Nephrotic range proteinuria was the most common indication for biopsy (59.9%) followed by unexplained renal dysfunction (28.5%) Nephritic syndrome and isolated haematuria were unusual indications in this adult cohort (1.1% and 0.8%, respectively).

Secondary glomerular diseases were the most common histological diagnosis in this series (229 cases, 61.6%); primary glomerular diseases accounted for 112 cases (30.1%); non-glomerular pathologies accounted for the remaining 31 biopsies (8.3%) (Figure 1).

Key: *ATN, acute tubular necrosis; CIN, chronic interstitial nephritis; DKD, diabetic kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HT, hypertensive change;, LN, lupus nephritis; MCN, minimal change nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis. "Other" in primary glomerular disease comprises mesangioproliferative glomerulonephritis and IgA nephropathy; "Other" in secondary glomerular disease comprises ANCA vasculitis, anti-GBM disease, immunotactoid glomerulopathy, light chain deposition disease, and cast nephropathy.*

HIV-associated glomerular diseases were the most common pathology encountered amongst secondary glomerulopathies (121 cases, 47.4% of secondary glomerulopathies) followed by lupus nephritis (36 biopsies, 31.4%) and glomerular injury due to hypertension (36 biopsies comprising 17 cases of malignant hypertension and 19 cases of benign hypertensive change, 15.7%), diabetic kidney disease accounted for 15 biopsies (6.6%). Sixteen cases (7.0%) of idiopathic proliferative glomerulonephritis, including 2 cases of idiopathic crescentic glomerulonephritis were recorded; ANCA-associated vasculitis and anti-glomerular basement membrane (anti-GBM) disease were extremely rare accounting for 1 case each. Other rare secondary disease processes in this cohort comprised immunotactoid glomerulopathy, light chain deposition disease, and cast nephropathy (1 case each).

The most common primary glomerular disease diagnosis in this series was focal segmental glomerulosclerosis (40 cases, 35.7% of primary glomerulopathies), followed by membranous nephropathy (25 cases, 22.32%), membranoproliferative glomerulonephritis (22 cases, 19.64%), and minimal change nephropathy (19 cases, 19.96%). Mesangioproliferative glomerulonephritis and IgA Nephropathy were rare diagnoses in this series (4 and 2 cases respectively)

Non-glomerular injury in this series comprised 14 cases of chronic interstitial nephritis (14.2% of non-glomerular diagnoses), 9 (29.0%) cases of reflux nephropathy, and 8 (25.8%) cases of acute tubular necrosis of various aetiologies.

Table 2: Comparison of histological diagnostic categories

	Primary glomerular (n = 112)	Secondary glomerular (n = 229)	Non-glomerular (n = 31)
Sex			
Male	62 (55.4%)	115 (50.2%)	16 (51.6%)
Female	50 (44.6%)	114 (49.8%)	15 (48.4%)
Age (years)	**33 [27–45]**	**34 [27–43]**	**36 [30–53]**
Ethnicity			
Black African	88 (78.6%)	195 (85.1%)	26 (83.9%)
White	11 (9.8%)	27 (11.8%)	3 (9.7%)
Indian	11 (9.8%)	5 (2.2%)	1 (3.2%)
Mixed ethnicity	1 (0.9%)	2 (0.9%)	0
Asian	1 (0.9%)	0	1 (3.2%)
Indication to biopsy			
Nephrotic range proteinuria	87 (77.7%)	122 (53.3%)	14 (45.2%)
Unexplained renal dysfunction	13 (11.6%)	78 (34.1%)	15 (48.4%)
Subnephrotic proteinuria	10 (8.9%)	25 (10.9%)	1 (3.2%)
Nephritic syndrome	1 (0.9%)	3 (1.3%)	0
Isolated haematuria	1 (0.9%)	1 (0.4%)	1 (3.2%)
Laboratory parameters			
Serum creatinine (μmol/L)	112 [77.5–219.5]	191 [90–529]	368 [162–690]
Serum cholesterol (mmol/L)	7.7 [5.0–11.2]	4.9 [3.8–6.1]	5.9 [5.0–9.3]
Urine protein: creatinine ratio (g/mmol)	0.69 [0.38–1.10]	0.43 [0.20–0.88]	0.47 [0.08–0.95]
Urine white cell count (cells/mm^3)	23500 [8000–68000]	18000 [7000–72000]	47500 [18000–87000]

The presentation of broad categories of histological diagnoses are compared in Table 2 below. There were no differences in gender (p = 0.671) or age (p = 0.427) of patients between the broad histological categories of injury in this series, although patients of Black African descent were the most frequent population group across all histological groups. White patients were diagnosed with secondary glomerular disease more frequently than with primary or non-glomerular pathologies, and Indian patients were more frequently diagnosed with primary glomerular disease. The relative frequencies of indications for biopsy showed variation between diagnostic categories. The majority (77.7%) of biopsies demonstrating primary glomerular disease presented with clinical features of the nephrotic syndrome compared to 53.3% of those with secondary glomerular disease and 45.2% of those with non-glomerular pathology. Unexplained renal dysfunction was the indication for biopsy in 34.1% of those classified as secondary glomerular disease compared to 11.6% of primary glomerular and 48.4% of non-glomerular pathologies (p < 0.001). Median urine protein: creatinine ratio was higher at biopsy in those patients subsequently diagnosed with primary glomerular disease (p = 0.008) and significant difference was observed for median creatinine across these groups (p < 0.001); urine white cell count did not show significant difference between histological categories (p = 0.243).

The presentations of the major primary glomerulopathies are compared in Table 3 below. A preponderance of male patients was noted in primary membranoproliferative glomerulonephritis (male to female ratio of 7:4). For all other histological types, the male to female ratio was approximately 1:1. Most patients in the focal segmental glomerulosclerosis (FSGS), membranous (MN), minimal change (MCN), membranoproliferative (MPGN), and mesangioproliferative (MesPGN) groups were of Black African descent. In the IgA nephropathy (IgAN) group, there were equal numbers of Black African and non-Black patients. Some disparity in patient age was observed between the biopsy groups, with MPGN and MCN diagnoses demonstrating a younger median age at diagnosis compared to FSGS, MesPGN glomerulonephritis and MN (p = 0.004). For patients aged 18–40 years and for those older than 60 years the most common primary glomerular lesion was that of FSGS; for patients aged 40–60 years membranous glomerulopathy was the most common lesion.

Nephrotic range proteinuria was the most common indication for biopsy in FSGS, MN, MCN and MPGN histological; unexplained renal dysfunction was a not uncommon indication in FSGS (25%) and was the most common indication in IgA nephropathy.

Renal function as indicated by median creatinine was generally preserved in MCN, MN, and MesPGN (median creatinine 72μmol/L) diagnoses but abnormal in FSGS and MPGN (p < 0.001). Urine protein: creatinine ratio was similar across all groups except in cases of MesPGN where proteinuria was relatively less significant (median

Table 3: Comparison of major primary glomerular diseases

	FSGS (n = 40)	**MN (n = 25)**	**MPGN (n = 22)**	**MCN (n = 19)**
Sex				
Male	21 (52.5%)	13 (52.0%)	14 (63.6%)	10 (52.6%)
Female	19 (47.5%)	12 (48.0%)	8 (36.4%)	9 (47.4%)
Age (years)	**37 [29–49]**	**43 [33–58]**	**28 [25–32]**	**31 [23–41]**
Ethnicity				
Black African	28 (70.0%)	19 (76.0%)	19 (86.4%)	17 (89.5%)
White	6 (15.0%)	3 (12.0%)	0	1 (5.3%)
Indian	4 (10.0%)	3 (12.0%)	3 (13.6%)	1 (5.3%)
Mixed ethnicity	1 (2.5%)	0	0	0
Asian	1 (2.5%)	0	0	0
Indication to biopsy				
Nephrotic range proteinuria	28 (70.0%)	22 (88.0%)	19 (86.4%)	16 (84.2%)
Unexplained renal dysfunction	10 (25.0%)	0	0	1 (5.3%)
Subnephrotic proteinuria	5 (5.0%)	3 (12.0%)	2 (9.1%)	2 (10.5%)
Nephritic syndrome	0	0	1 (4.5%)	0
Isolated haematuria	0	0	0	0
Laboratory parameters				
Serum creatinine (μmol/L)	148.5 [104–327]	93 [64–123]	145 [83–221]	78 [53–105]
Serum cholesterol (mmol/L)	9.3 [6.5–13.0]	7.5 [4.4–10.1]	5.4 [4.1–7.7]	11.1 [8.4–14.7]
Urine protein: creatinine ratio (g/mmol)	0.71 [0.38–1.36]	0.67 [0.38–1.17]	0.63 [0.34–1.10]	0.69 [0.44–1.00]
Urine white cell count (cells/mm^3	36000 [8000–72000]	22500 [8000–35000]	36000 [21000–79000]	22000 [13000–66000]

UPCR 0.21g/mmol). No statistically significant difference was detected for leukocyturia (p = 0.166). Median serum cholesterol was highest in those patients diagnosed with MCN (11.1 mmol/L) and lowest in those with MPGN (5.4 mmol/L) and differences in serum cholesterol between primary glomerulopathies was significant (p = 0.017).

DISCUSSION

This study expands the literature on kidney injury patterns detected on biopsy in South Africa. The significant contribution of HIV to glomerular disease is highlighted, and patterns of primary glomerular disease reported previously in Johannesburg are confirmed. Although subtle clinical variation exists between histological diagnoses, considerable overlap in laboratory parameters highlights the importance of biopsy as an investigative technique.

The overall contribution of primary glomerular disease in this study (30.1%) parallels that reported by other South African studies (31.2%–39.7%).(7–9) Secondary glomerular disease contributed to 62% of included biopsies in this series, compared to 49% reported in the local literature.(7–9) Lupus nephritis (LN) and HIV-associated glomerulopathies comprised more than half of these cases. The seroprevalence of HIV infection in the local population is likely to have contributed substantially to the prevalence of secondary glomerular disease in this study. Adherence to practices which advocate biopsy in patients known with systemic lupus erythematosus at low levels of proteinuria is a factor in the significant number of LN cases recorded.

Unexplained renal dysfunction was the second most common indication for biopsy, informing the contribution of hypertensive and non-glomerular injury patterns in this series. The relatively low prevalence of diabetic nephropathy in this series is likely explained by local practices which eschew biopsy in cases where diabetic nephropathy is the probable aetiology. The comparatively low prevalence of non-lupus glomerulonephritis in the present study may have arisen from the relative low incidence of this pathology in adults as compared to paediatric patients.

FSGS has been reported to be the most common glomerular injury in other studies undertaken in South Africa and the developing world;(6–9,11–14,15,16,17) Black African patients are known to be at increased risk of FSGS due to the penetrance of APOL1 risk alleles in this population which confer a 17-fold risk for the disorder.(18) FSGS associated with APOL1 has also been associated with a younger age of onset and faster progression to kidney failure.(18) The population of the present study is predominantly of Black African descent and is broadly reflective of the ethnic variation of Gauteng as reported by Statistics SA.(19) Local population genetic risk may therefore partly account for the significant proportion of primary FSGS cases. In comparison, a preponderance of MPGN has been

reported by researchers in Cape Town,(7) possibly reflecting geographical variations in ethnic composition.

Local biopsy practices may have contributed to the profile of glomerular disease in the present study: IgA nephropathy has been reported to be the most common glomerular disease in other programmes in which haematuria is a more frequent indication for investigation. (1,7,20–29). Identification of cases of persistent microscopic haematuria for biopsy requires an effective urinalysis screening programme which beyond the capacity of South Africa, so that the contribution of IgA nephropathy to glomerular disease in these settings is uncertain.

The median age of patients in this series was 34 years and that of patients diagnosed with primary glomerular disease was 33 years, similar to that reported in other studies.(8,9,21) The tendency of MesPGN, MPGN, and MCN to affect younger patients and MN to affect older patients as observed in this study is well described in the literature. (30)A significant male dominance was observed in MPGN, for all other primary glomerulopathies no significant gender disparity was observed; a slight male preponderance was observed overall for patients undergoing native kidney biopsy. Census data indicates that males constitute 50.2% of the Gauteng population;(19) the slight male preponderance in the present study may reflect gendered differences in healthcare-seeking behaviour, however, other series have reported similar male predominance in primary glomerular pathologies.(14,15)

The highest median creatinine values were recorded in patients with MPGN and FSGS. Renal insufficiency is known to be common at presentation with FSGS, occurring in 30-45% of cases and studies have shown renal function to be most severely affected in FSGS.(31,32) Serum creatinine at biopsy is predictive of progression to kidney failure.(33) Structural alterations to the effective glomerular filtration surface in both pathologies contribute to the observed renal dysfunction. In contrast, eGFR at presentation of MCN is usually preserved.(31,32,34).

Although no significant difference was observed for proteinuria, other series have suggested proteinuria to be more severe at presentation in MCN.(31,32) Multiple factors may have contributed to the lack of discriminant effect of proteinuria observed, including nutritional status of individual patients, antecedent empiric treatment, and severity of filtration impairment by established glomerulosclerosis.

No significant difference was observed for leukocyturia across primary glomerulopathy diagnoses in this study. Whilst proteinuria may cause mild leukocyturia through the mechanism of tubular injury-induced interstitial nephritis, significantly elevated urinary white cell count is more characteristic of the glomerulonephritides.(35) Restriction of the definition of primary glomerular disease to podocytopathies and the lack of significant difference in proteinuria between these groups likely contributed to the similarity in leukocyturia between these groups.

Serum cholesterol was highest in those patients diagnosed with MCN and lowest in those with MPGN. A similar distribution of dyslipidaemia has been reported by others.(31)

LIMITATIONS

There are limitations to this study including the fact that a single-centre nature of the sample cohort may limit generalizability. Nevertheless, the findings are broadly consistent with previous reports from Johannesburg. Additionally, sampling bias may have occurred due to missing data and thus exclusion from the study and the tendency for patients with proteinuria to present for biopsy. Finally, interpretation of the presented patterns of glomerular disease should be contextualised in the framework of biopsy practices.

CONCLUSIONS

Glomerular disease primarily affects young patients. Secondary glomerular disease is more common than primary pathologies, with HIV infection contributing significantly to the prevalence of the entity in the local study context. Primary glomerulopathies typically present with the nephrotic syndrome and with relatively preserved renal function with focal segmental glomerulosclerosis being the most frequently diagnosed primary glomerulopathy. A relatively increased serum creatinine at biopsy may distinguish primary glomerulopathies with more severe histological injury. Despite the observed trends in laboratory variables, diagnostic utility thereof in distinguishing glomerular disease is unclear. This study demonstrates the variability in glomerular pathologies and as such emphasizes the importance of biopsy in ensuring appropriate treatment to reduce the risk of progression to kidney failure.

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CONFLICT OF INTEREST

The Authors have no conflict of interest to declare

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DAGLIF 10	Dapagliflozin	10 mg	30	S4	Tablet	3006122001	6009697620038	R260.87	R300.00

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If further information is required, please refer to the Professional Information Leaflet approved by SAPRHA (3 August 2022).

Yours sincerely,

Rama Subramanian
Country Head

S4 Daglif 5MG 10MG
DAPAGLIFLOZIN

S4 **DAGLIF 5** film-coated tablets. Each film-coated tablet contains 5 mg dapagliflozin. Reg No. A55/21.2/0049
S4 **DAGLIF 10** film-coated tablets. Each film-coated tablet contains 10 mg dapagliflozin. Reg No. A55/21.2/0050

For full prescribing information refer to the approved package insert. Zydus Healthcare SA (Pty) Ltd. Block B, Southdowns Office Park, 22 Karee Street, Centurion, 0157. Tel: +27 (0)12 748 6400.
DAG/04/23.