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DISSERTATION

DIABETIC NEPHROPATHY IN A TERTIARY CLINIC IN SOUTH AFRICA, A CROSS-SECTIONAL STUDY

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DECLARATION OF AUTHORSHIP

I hereby declare that this work is original and where other's people work has been used, this has been properly acknowledged and referenced. Neither this work, nor any part of it, is to be or has been submitted for another degree at this or any other University.

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACR	Albumin-to-creatinine ratio
BP	Blood pressure
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HbA_{1C}	Haemoglobin A_{1C}
HDL	High-density lipoprotein
IDF	International Diabetes Federation
LDL	Low-density lipoprotein
MDRD	Modification of Diet in Renal Disease Study
SEMDSA	Society for Endocrinology, Metabolism, and Diabetes of South Africa

ORIGINAL ARTICLE

COVER PAGE

Article title: **Diabetic nephropathy in a tertiary care clinic in South Africa, a cross-sectional study.**

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Microalbuminuria; diabetes control; estimated glomerular filtration rate; HbA_{1C}

ABSTRACT

Objective: The aim of this study was to determine the prevalence of micro- or macroalbuminuria among type 1 and type 2 diabetic patients and to examine the relationship with diabetes control parameters: haemoglobin A1C (HbA_{1C}), blood pressure (BP) and lipids.

Design: Analytical cross-sectional study.

Setting and subjects: The study consisted of 754 patients with either type 1 or type 2 diabetes mellitus, attending a diabetic clinic at the Kalafong Hospital in Pretoria, South Africa.

Outcome measures: Micro- or macroalbuminuria and estimated glomerular filtration rate (eGFR).

Results: Of all patients, 88.9% had HbA_{1C} > 7%, and 81% had low-density lipoprotein (LDL) cholesterol ≥1.8 mmol/l. Overall prevalence of micro- or macroalbuminuria was 33.6%. Logistic regression revealed that HbA_{1C}, duration of diabetes, systolic BP, male sex and triglycerides predicted microalbuminuria.

Conclusion: The prevalence of micro- or macroalbuminuria in this study falls within the ranges of what has been previously reported in Africa. In all patients, HbA_{1C} and duration of diabetes were the strongest predictors of microalbuminuria, and age was the strongest predictor of a low eGFR. Diabetes was poorly controlled, making the progression to end-stage renal failure a real concern in these patients.

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Introduction

In 1901, diabetes mellitus was described as “very uncommon” in Africa.[1] Today, the situation is different. According to the International Diabetes Federation (IDF) atlas, 19.8 million people had diabetes in 2013 in Africa,[2] and the number of patients is increasing. Diabetes in Africa is associated with a higher complication rate than in developed countries, including diabetic nephropathy.[3,4]

Diabetic nephropathy is the major cause of end-stage renal disease (ESRD) in developed countries (~30% of cases).[5,6] In the near future, diabetic nephropathy is expected to become the most frequent cause of ESRD in the developing world.[7] About 20% to 30% of people with either type 1 or type 2 diabetes develop nephropathy, whose incidence increases with the duration of diabetes.[5] Certain ethnic groups (Native Americans, Mexican Americans, and African Americans) demonstrate a higher prevalence rate of severe nephropathy in comparison to Caucasians.[5,6]

In Africa, the prevalence of diabetic nephropathy ranges from 32% to 57% and overt proteinuria is found in 5% to 28% of diabetic patients.[3,8] Furthermore, diabetes mellitus contributes to a third of all patients in dialysis units in Africa.[8] Diabetic nephropathy is a major public health concern, because dialysis and kidney transplantation therapy are almost completely inaccessible to most diabetic patients in Africa.[9] Already, a 12-year follow-up study conducted in South Africa in a cohort of type 2 diabetic patients showed that ESRD was a major cause of death in 29% of patients predominantly non-Caucasian.[10] Once a patient reaches the renal-failure stage, therapeutic options are limited given the severe shortage of dialysis slots in South Africa. Therefore measures to prevent kidney disease are crucial. Early medical interventions and lifestyles changes such as reduction of protein intake and smoking cessation have been shown to slow the progression from microalbuminuria to overt proteinuria and eventually ESRD. Furthermore, there is impressive experimental and clinical evidence that angiotensin-converting enzyme (ACE) inhibitors have specific renoprotective properties in patients with diabetic or non-diabetic renal disease who have proteinuria.[11]

The aim of this study was to: determine the prevalence of diabetic nephropathy (micro- or macroalbuminuria) among type 1 and type 2 diabetic patients who attended the Kalafong Diabetes Clinic in Pretoria (South Africa); and examine the relationship between diabetes control parameters including haemoglobin A_{1C} (HbA_{1C}), blood pressure (BP) levels and lipids and diabetic nephropathy in this group of predominantly African patients with diabetes.

Method

Study design

The study was an analytical cross-sectional study.

Setting

The study was conducted at Kalafong Hospital, which is a tertiary public hospital in Pretoria, Gauteng province (South Africa). The hospital serves as a training site for the Faculty of Health Sciences of the University of Pretoria. Patients seen at the Kalafong Diabetes Clinic are usually referred on the basis of two criteria: firstly, either poorly controlled diabetes or BP; or, the presence of diabetic complications.

Subjects

Data were extracted from the electronic database of the Kalafong Diabetes Clinic of all patients who attended the clinic from January to December 2012. Patients were excluded from the study if they were under 18, had either secondary or uncertain type diabetes, or had nephropathy stemming from other causes. Patients were also excluded if they attended the clinic only once in 2012 or if they did not have at least one or more of the following measurements done: HbA_{1C}, serum creatinine and urine albumin-to-creatinine ratio (urine ACR).

Approval for the study was obtained from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria (154/2013).

Measurements

Every patient who attends the Diabetes Clinic is scheduled for a minimum of four visits per year (one every three months). Kidney function is assessed twice a year (every six months) with a serum creatinine and urine ACR on a random urine sample. HbA_{1C} concentration, serum concentrations of creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides are measured in peripheral blood; and low-density lipoprotein (LDL) cholesterol is calculated using the Friedewald formula. All BP measurements were taken with an electronic BP machine (EDAN Vital Signs Monitor, model M3A).

Statistical analysis

Data were statistically analysed by means of STATA® version 12 (StataCorp LP, College Station, USA) and IBM SPSS® Statistics version 22 (IBM Corporation, Somers, NY). Descriptive statistics were done for all variables with appropriate methods based on the type

and the distribution of the data. Frequency tables, cross tabulation and Chi square tests were used. Logistic regression was performed to determine which predictor variables influence the outcome.

Logistic regression was conducted as follows: univariate logistic regression was done for all of the following variables: sex, race (dummy variables were created for Black, White, Indian and Coloured patients), age, type of diabetes, snuff use, cigarette smoking, BMI, duration of diabetes, duration of hypertension, HbA_{1C}, total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, mean systolic BP, mean diastolic BP, use of ACE inhibitors, coefficient of variance of systolic BP measurements and coefficient of variance of diastolic BP measurements (as indicators of BP variation).

All variables with a p-value of more than 0.2 in a univariate analysis were excluded from the multivariable logistic regression. All analysis was consecutively done, dropping variables from the preceding model that contributed the least to the overall performance of the model until the most parsimonious model was obtained with the least number of predictor variables.

The dependent variables were the estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 (Stage 2 Chronic Kidney Disease and above) and microalbuminuria based on urine ACR of more than 2.5 for males and 3.5 for females. The eGFR was calculated by using the Modification of Diet in Renal Disease Study (MDRD) equation: eGFR (ml/min/1.73m^2) =186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if Black).[12] This multivariate analyses were done for type 1 and type 2 diabetic patients combined and for both groups separately.

Results

The study population was all 798 diabetic patients who had attended the Kalafong diabetic clinic in 2012. In 2012, the number of visits attended per patient on average was 4.09 (±0.92), ranging from 1 to 6 visits. Of all patients 44 were excluded: 8 were < 18 years old, 11 attended only one visit or lacked information (such as HbA_{1C}, serum creatinine or urine ACR), and 25 had secondary diabetes or the type of diabetes was uncertain (Figure 1).

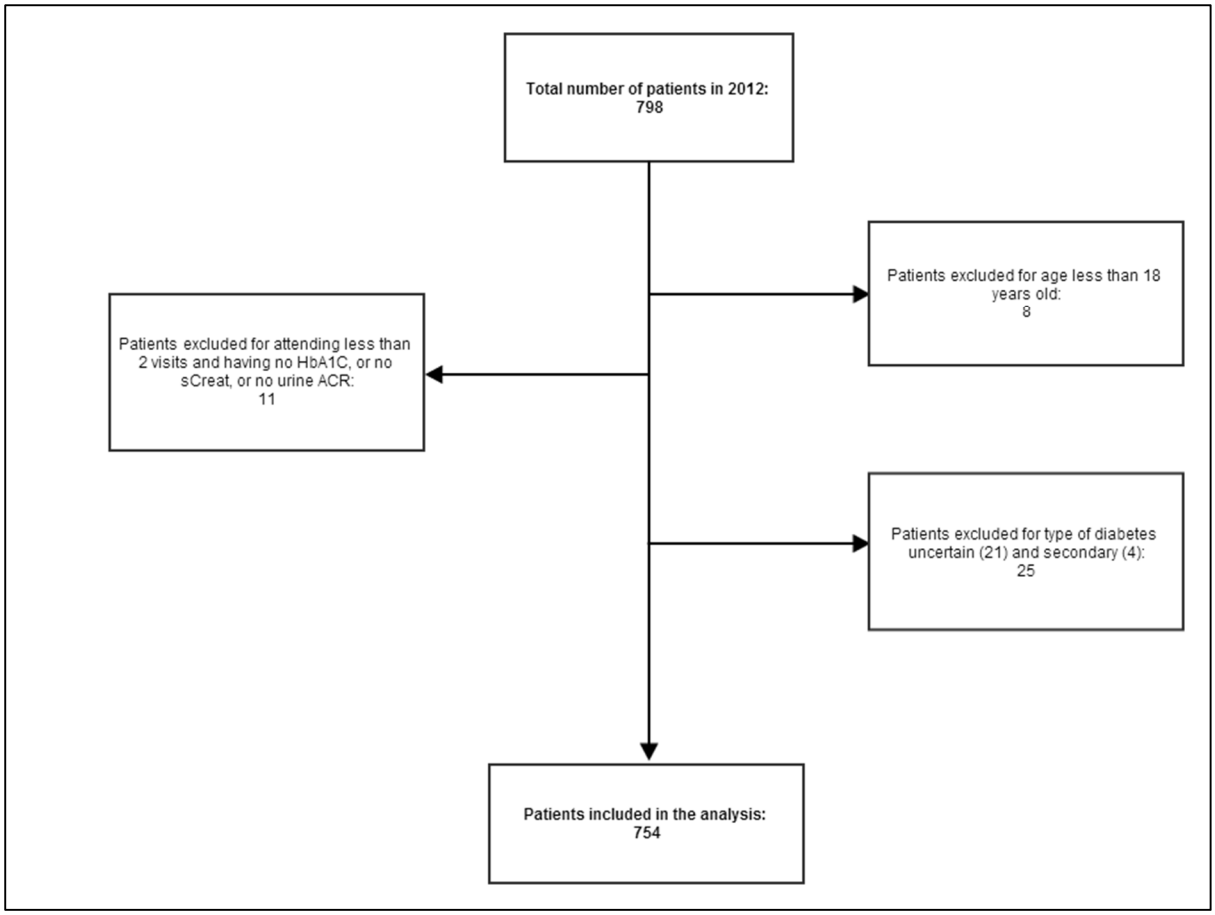

Figure 1: Flow chart of patients included in the study

Demographic and clinical characteristics of the 754 patients who fulfilled the inclusion criteria are reported in Table I.

The patients were predominantly black (91.1%) and female (62.9%) with a mean age of 57.2 (±14.9) years old. The majority of the 754 patients (66.6%) had type 2 diabetes. The median duration of diabetes was 11 years. Most patients (71.8%) had never smoked and 10.5% were current smokers at the time of data collection. The majority of patients (84.4%) were classified as overweight and obese with a mean BMI of 31.5 (±6.7) kg/m^2. High BP was diagnosed in 79.2% of the patients, of which 75.1% were receiving ACE inhibitors.

Table I: Clinical characteristics of diabetic patients who attended the clinic in 2012

Characteristics	N (N=754)	Statistics
Age		Mean = 57.2 SD = 14.9
Gender		
Male	280	37.1%
Female	474	62.9%
Race		
Black	687	91.1%
White	27	3.6%
Coloured	3	0.4%
Indian	37	4.9%
Diabetes type		
Type 1	252	33.4%
Type 2	502	66.6%
Duration of diabetes		Range = 0 to 64 years Median = 11 years (IQ - 6 to 18)
Smoking status		
Current	79	10.5%
Never	541	71.8%
Stopped	130	17.2%
Unknown	4	0.5%
Snuff use		
Yes	62	8.2%
No	666	88.3%
Unknown	26	3.5%
BMI	734	Mean = 31.5 SD = 6.7
Underweight (<18.5)	8	1%
Normal (18.5-25)	107	14.6%
Overweight (25-30)	214	29.2%
Obese class 1 (30-35)	199	27.1%
Obese class 2 (35-40	129	17.6%
Obese class 3 (>40)	77	10.5%
Hypertension*	597	79.2%
Unknown	2	0.3%
Duration of hypertension	595	Range = 0 to 62 years Median = 11 years (IQ – 7 to 18)
ACE inhibitor use	566	75.1%

*Hypertension >140mmHg systolic and/or 90mmHg diastolic

In Table II, patients are compared according to their type of diabetes. As expected type 1 patients were significantly younger than type 2 patients (mean age 46.5 vs 62.6 years, p-value <0.001), had shorter known duration of diabetes (11.4 vs 13.4, p-value =0.003) and had lower frequencies of hypertensive disease (57.1% vs 90.2%, p-value <0.001).

Table II: Description of the study population according to their type of diabetes.

Characteristics		Type 1 n = 252	Type 2 n = 502	p-value
Age in years, mean (SD)		46.5 (15.6)	62.6 (11.3)	< 0.001
Gender, n (%)	Male	122 (48.4)	158 (31.5)	< 0.001
	Female	130 (51.6)	344 (68.5)	
Race, n (%)	Black	235 (93.3)	452 (90)	0.001
	White	14 (5.6)	13 (2.6)	
	Coloured	0	3 (0.6)	
	Indian	3 (1.2)	34 (6.8)	
Smoking status, n (%)	Current	36 (14.3)	43 (8.6)	0.08
	Never	169 (67)	372 (74.1)	
	Stopped	46 (18.3)	84 (16.7)	
	Unknown	1 (0.4)	3 (0.6)	
Snuff use, n (%)		17 (6.8)	45 (9)	0.121
	Unknown	13 (5.2)	13 (2.6)	
Duration of diabetes in years, mean (SD)		11.4 (8.3)	13.4 (8.4)	0.003
BMI, mean (SD)		29.3 (6.5)	32.5 (6.5)	<0.001
Hypertension, n (%)		144 (57.1)	453 (90.2)	< 0.001
	Unknown	2 (0.8)	0	
Duration of hypertension, mean (SD)		11 (8)	14.2 (9)	<0.001
ACE inhibitor use, n (%)		169 (67.1)	397 (79.1)	< 0.001

Evaluation of diabetes control parameters: HbA_{1C}, BP and lipids

The HbA_{1C} of patients ranged between 5.4% and 22.5%, with a median of 9.6%. The mean systolic BP was 140.4 (±16.9) mmHg, and the mean diastolic BP was 80.9 (±9.8) mmHg. The medians for total cholesterol, triglycerides and LDL were 4.4 mmol/l, 1.4 mmol/l and 2.5 mmol/l respectively (Table III).

Table III: Diabetes control parameters

Variables	N	Statistics
HbA_{1C} (%)	745	Range = 5.4 to 22.5 Median = 9.6 (IQ – 7.8 to 11.8)
BP (mmHg)	754	
Systolic BP[#]		Mean = 140.4, SD = 16.9
Diastolic BP[≠]		Mean = 80.9, SD = 9.8
Lipids (mmol/l)		
Total cholesterol	706	Median = 4.4, IQ: 3.7 to 5.2
Triglycerides	702	Median = 1.4, IQ: 0.9 to 2.1
LDL*	690	Median = 2.5, IQ: 1.9 to 3.1

[#]Systolic BP: Good <140mmHg, Moderate 140-160mmHg, Poor >160mmHg; [≠]Diastolic BP: Good <80mmHg, Moderate 80-100mmHg, Poor >100mmHg; *LDL was calculated with the Friedewald formula. LDL could not be calculated in a number of patients who had very high triglycerides

A small proportion of the study population (11.1%) met the HbA_{1C} targets (HbA_{1C} <7%), 13.8% type 1 patients and 9.8% type 2 patients. About half of type 1 patients (50.4%) recorded an HbA_{1C} over 10%. More than 66% of type 1 patients had a good systolic BP, against 49.2% of type 2 patients. Most patients (96.2%) had a diastolic BP of less than 100 mmHg. All patients had relatively good total cholesterol and triglycerides levels, but 79.5% of patients had LDL levels equal to or more than 1.8 mmol/l.

Assessment of the renal function of patients: urine ACR and eGFR

Table IV: Assessment of renal function using eGFR and urine ACR.

Variables	N	Statistics
Urine ACR (mg/mmol)	735	Range = 0.0001 to 977 Median = 1.3 (IQ: 0.6 to 5.6)
Normal <2.5 (Male); 3.5 (Female)	488	66.4%
Microalbuminuria 2.5-25 (Male); 3.5-35 (Female)	169	23%
Macroalbuminuria >25 (Male); >35 (Female)	78	10.6%
eGFR (MDRD) (ml/min/1.73m^2)	721	Range = 1.99 to 430.56 Median = 102.31 (IQ: 71.4 to 138.96)
>60 ml/min/1.73m^2	721	82.7%
<60 ml/min/1.73m^2		17.3%

Of the study population 66.4% had a normal urine ACR, meaning less than 2.5 mg/mmol for males and 3.5 mg/mmol for females. The median recorded urine ACR for both sexes was

1.3 mg/mmol. The prevalence of microalbuminuria was 23%. The eGFR of the patients using the MDRD formula ranged between 1.99 and 430.56 with a median of 102.3 ml/min/1.73m^2. A low eGFR (<60 ml/min/1.73m^2) was recorded in 17.3% of patients.

Logistic regression analysis:

Logistic regression analysis was conducted to determine which predictor variables influence the outcome: microalbuminuria (urine ACR) and low eGFR (< 60 ml/min/1.73m^2) in all patients, then in type 1 only and finally in type 2 only.

Prediction success achieved for microalbuminuria among all patients was 75.1% with a model Chi square of 146.986 (p-value <0.001). The variables systolic BP (p-value <0.001), HbA_{1C} (p-value <0.001), duration of diabetes (p-value <0.001), triglycerides (p-value =0.008) and male sex (p-value <0.001) made a significant contribution to the prediction. Thus, if the values of systolic BP, HbA_{1C}, duration of diabetes and triglycerides are raised by one unit, the odds of obtaining microalbuminuria are more likely to increase. The use of ACE inhibitors did not seem to have an influence on microalbuminuria as measured by the urine ACR.

Prediction success for eGFR in all patients was 69%. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between diabetic patients with eGFR <60 ml/min/1.73m^2 and the others (Chi square = 122.555, p-value <0.001). Nagelkerke's R^2 of 0.213 indicated a moderate relationship between prediction and grouping. The independent variables that contributed significantly to the prediction were age (p-value <0.001), duration of hypertension (p-value =0.022) and being Indian (p-value =0.005). It should be noted that an unexpected difference was demonstrated for predictors of urine ACR and eGFR. The number of Indian patients was small in the study. Despite this small number, it was still a significant predictor of lower eGFR.

A logistic regression analysis was conducted to predict microalbuminuria among type 1 diabetic patients only. The model chi square had a value of 49.678 and a p-value <0.001. The Hosmer-Lemeshow (H-L) goodness-of-fit test statistic was greater than 0.05; the model was, therefore, quite a good fit. HbA_{1C} (p-value <0.001), duration of diabetes (p-value <0.001) and triglycerides (p-value <0.001) contributed significantly to the model. In this model the use of ACE inhibitors seemed to play a non-significant protective role.

Prediction success for eGFR worse than stage 1 was 79.3%. The H-L goodness-of-fit test was 0.055, which means that the estimate of the model fitted the data at an acceptable level. Age (p-value <0.001), systolic BP (p-value =0.022) and coefficient variation of diastolic BP (p-value =0.008) significantly contributed to the model.

Finally, logistic regression analysis to predict eGFR <60 ml/min/1.73m^2 and microalbuminuria among type 2 patients was conducted. Overall prediction successes were 73% and 65% for microalbuminuria and eGFR respectively.

For microalbuminuria among type 2 patients, the independent variables that contributed significantly to the prediction were HbA_{1C} (p-value <0.001), duration of diabetes (p-value <0.001), systolic BP (p-value <0.001), male sex (p-value <0.001) and ACE inhibitors (p-value =0.025). According to the model, the use of ACE inhibitors was negatively associated with microalbuminuria, thus protective (OR =0.558; 95% CI: 0.336 - 0.928).

The independent variables that seemed to have made a significant contribution to the prediction for eGFR were age (p-value <0.001) and Indian descent (p-value =0.008). From the above-mentioned models it seems that protection related to Indian descent with regard to eGFR is only valid in type 2 diabetic patients, probably because of the very few Indian patients with type 1 diabetes.

Discussion

This analytic cross-sectional study with a study population of 798 diabetic patients attending a tertiary care diabetes clinic in Pretoria (South Africa) provided the opportunity to determine the prevalence of micro- or macroalbuminuria, and to examine the relationship between microalbuminuria and putative risk factors.

Glycaemic control as measured by the HbA_{1C} was poor. More than 88% of patients did not meet the HbA_{1C} target of below 7% as recommended by the 2012 South African Society for Metabolism, Diabetes and Endocrinology (SEMDSA) guidelines. In a cluster-randomised trial conducted in the Tshwane district, Webb et al found that more than 70% of patients had an HbA_{1C} value above 7%.[13] In another study conducted in a South African population with type 2 diabetes, 73.8% of patients failed to meet the HbA_{1C} target.[14] Poor glycaemic control has also been reported in other parts of sub-Saharan Africa (Cape Town, Northern Ethiopia and Kenya).[15-17]

Lipid control was poor, with 81% of patients having LDL-cholesterol value above 1.8 mmol/l. Webb et al reported similar results, with more than 80% of their study population having uncontrolled lipids.[13]

In this study, the mean systolic BP was 140 mmHg and the mean diastolic BP was 80 mmHg. More than half of the patients (54%) had a diastolic BP above the target recommended by 2012

SEMDSA guidelines. Webb et al reported a slightly higher mean systolic BP and mean diastolic BP – 43 mmHg and 85 mmHg respectively.[13] However, Gill et al recorded lower mean systolic BP (108 mmHg) and mean diastolic BP (72 mmHg) compared to this study.[16]

In the present study, 84.4% of patients were overweight, including 55.2% who were obese. Webb et al found similar levels of obesity in their study, where more than 80% of patients were overweight.[13]

One of the limitations of the present study is that it was a tertiary-clinic based study. The study population was mostly patients who were difficult to control at a lower level of care, and were therefore referred to the tertiary clinic. This difference in the patient population might have introduced some degree of referral bias, making it difficult to extrapolate the results to the general population or to primary health care diabetes management. However, two other studies conducted in South Africa also showed that diabetes control was suboptimal.[13,14] The first study was with diabetic patients attending primary health care clinics, but the study population from the second study was attending a diabetic clinic in a tertiary academic hospital similar to ours after referral by their treating physicians at the primary health care clinics.[13,14]

In this cross-sectional analysis, the prevalence of micro- or macroalbuminuria among patients with type 1 and type 2 diabetes was 33.6%; 23% for microalbuminuria and 10.6% for macroalbuminuria. In other studies, various frequencies of microalbuminuria have been found, ranging from 10.7% to 39%.[18-22] This variation in the frequency of microalbuminuria may be attributed to different factors such as methods of urine collection, differences in the populations and sample size, ethnic susceptibility to develop nephropathy and definitions of microalbuminuria.

The study reported in this paper showed a statistically significant relationship between microalbuminuria and both poor glycaemic control (HbA_{1C}) and duration of diabetes. This result was consistent when type 1 and type 2 diabetic patients were both included in the logistic regression models, but also when analysed separately.

Poor glycaemic control is a well-defined contributor to the development and progression of microalbuminuria among diabetic patients. Ghosh et al found that HbA_{1C} was strongly associated with microalbuminuria.[21] However, Lutale et al failed to demonstrate any significant relationship between the level of glycaemic control and microalbuminuria in a population of type 1 and type 2 diabetic patients in Tanzania.[22]

Ghosh et al could not demonstrate a significant correlation between microalbuminuria and the duration of diabetes, in contrast to the study reported in this paper.[21] These authors suggested that the absence of a significant correlation between microalbuminuria and diabetes duration could be due to the difficulty in dating the onset of diabetes.

High BP is known as the most significant contributing factor in the development of diabetic nephropathy in both type 1 and type 2 diabetic patients.[22] In the current study, systolic BP was significantly associated with microalbuminuria in type 2 diabetic patients and also when type 1 and type 2 diabetic patients were combined in the predictive model. Similar results were found in two studies conducted in Tanzania in 2007 and 2012, as well as in a cohort of African patients with type 1 diabetes in South Africa.[21-23]

Triglycerides were significantly correlated to microalbuminuria in logistic regression models for type 1 and type 2 patients combined and for type 1 diabetic patients only. Male sex was significantly predictive for microalbuminuria in logistic models for all diabetic patients and for only type 2 diabetic patients. Male sex has been previously found as a factor associated with high risk of nephropathy among type 2 diabetic patients.[11]

Although 10.5% of the patients were currently smoking tobacco, smoking was not predictive for either microalbuminuria or for a reduced eGFR in this study. The failure to provide evidence to confirm smoking as predictor of diabetic nephropathy could be explained by the low prevalence of smoking in the study population. Parving et al, who had a study population of 32 208 type 2 diabetic patients, found an association between micro-/macroalbuminuria and smoking (OR =1.15; 95% CI: 1.08 - 1.22). [19]

In the current study, the use of ACE inhibitors seemed to play a protective role in type 2 diabetic patients, yet non-significantly in type 1 diabetic patients. Seventy-five percent of the study population were on ACE inhibitors. Patients attending the Kalafong Diabetes Clinic did not receive ACE inhibitors only when they could not tolerate or had significant side effects from ACE inhibitors, or when they had normal BP without microalbuminuria. This may have contributed to confounding by indication or contra-indication. ACE inhibitor use is not commonly reported on in studies of diabetic nephropathy among African patients. In Pinchevsky et al study, 80% of all patients were receiving ACE inhibitors.[14] Ghosh et al found that hypertensive patients who are on ACE inhibitors or angiotensin receptor blockers (ARBs) were three times more likely to have normoalbuminuria compared to those using other anti-hypertensive medications.[21]

In this study, the median eGFR was 102.3 ml/min/1.73m^2 and 17% of the patients had more than stage 1 renal insufficiency (eGFR <60 ml/min/1.73m^2). These results are similar to those found in a cross-sectional study evaluating diabetic patients from 33 countries where the authors reported that eGFR was below 60 ml/min/1.73m^2 in 22% of the patients.[19]

A low eGFR (<60 ml/min/1.73m^2) was significantly associated with age in all models. The Indian race was predictive of lower eGFR. However, the number of patients of Indian descent was small in the study (37/754). Despite the small number, it was still a significant predictor of lower eGFR. This may be explained by the fact that patients of Indian descent have a lower muscle mass that can explain the lower eGFR.[24]

In the present study, micro- or macroalbuminuria was not always confirmed by two urine specimens contrary to most recommendations. However, a similar method has been used in other settings.[19,20]

One of the strengths of this study is the size of the study population.

Conclusion

The prevalence of micro- or macroalbuminuria in this study falls within the ranges of what has been previously reported in sub-Saharan Africa. In all patients, HbA_{1C} and duration of diabetes were the strongest predictors of microalbuminuria, and age was the strongest predictor of a low eGFR. Diabetes was poorly controlled, making the progression to end-stage renal failure a real concern in those patients. Therefore, the accent must be put on measures to prevent the progression of renal lesions: strict glycaemic control, smoking cessation, attainment of optimal BP, initiating lipid-lowering therapy, and decreasing urinary albumin excretion.

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JEMDSA
Journal of Endocrinology, Metabolism and Diabetes of South Africa

JEMDSA representation

The Journal of Endocrinology, Metabolism and Diabetes of South Africa (JEMDSA) is the official journal of **SEMDSA** (Society for Endocrinology, Metabolism and Diabetes of SA), **DESSA** (Diabetes Education Society of SA), **NOFSA** (National Osteoporosis Foundation of SA), **SASOM** (SA Society of Obesity and Metabolism), **LASSA** (Lipid and Atherosclerosis Society of SA) and **PAEDS-SA** (The Paediatric Endocrinology Society of SA).

SEMDSA has for many years strived to be an umbrella organisation for affiliated South African professional societies with a focus and scope in advancing research and education in the fields of endocrinology, metabolism and diabetes.

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JEMDSA aims to publish world-class scholarly work in endocrinology, metabolism and diabetes. The journal is accredited by the National Department of Education for the measurement of research output of public higher education institutions and earns research subsidies for South African academic departments.

Through stringent peer review, the journal also aims to make a regional contribution to the international knowledge base of endocrinology, metabolism and diabetes and hopes to also offer other African countries the opportunity to make a world-class African contribution.

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University of Pretoria
Faculty of Health Sciences
School of Health Systems and Public Health

Diabetic nephropathy and its association with diabetes control parameters in a tertiary care diabetes clinic

Research protocol submitted in partial fulfilment of the Master of Public Health Degree

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17 February 2015

Diabetic nephropathy and its association with diabetes control parameters in a tertiary care diabetes clinic

Executive Summary

Diabetes mellitus is a major global public health concern because of its high prevalence, along with its high mortality and morbidity. Low- and middle-income countries are not spared, with a contribution of over 80% of cardiovascular and diabetes deaths occurring in those settings. Diabetic nephropathy (DN) is the major cause of end-stage renal disease (ESRD) in developed countries such as the United States of America (USA) and Japan, and it is expected to be the most frequent cause of ESRD in the developing world including Africa.

Studies have shown that the frequency of renal complications of diabetes depends very much on race, but there is still a dearth of published studies focusing on DN in sub-Saharan Africa. Few studies have been conducted on DN in black Africans. Therefore, there is a paucity of data collected and a limited knowledge on DN in African populations.

The proposed study will be an analytical cross-sectional study. The study goal will be to examine the possibility of a relationship between diabetes control parameters (HbA1C, blood pressure level and lipids) and DN in African patients with diabetes. The researchers will perform a retrospective analysis of data collected in 2012 from the Kalafong Diabetes Clinic.

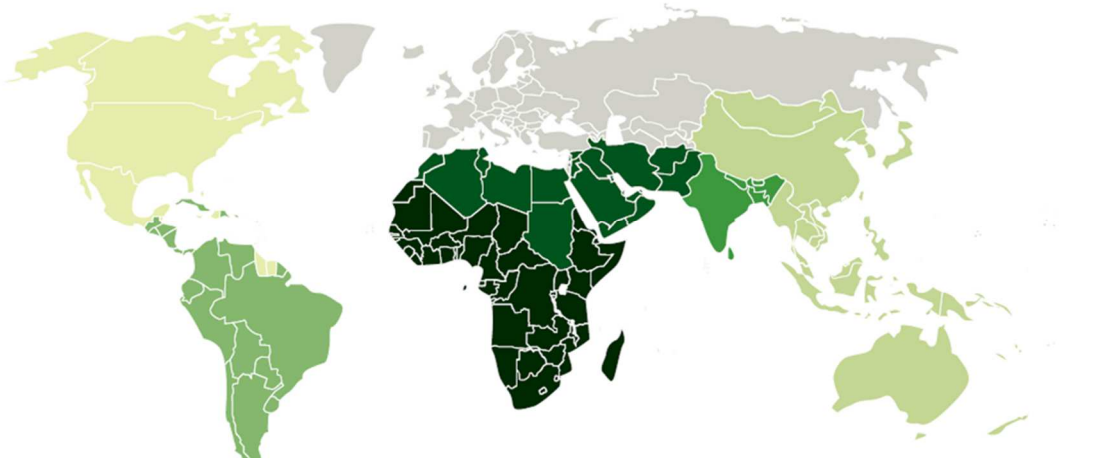
A better understanding of potential associations in Africans, especially when it comes to the role played by different risk factors, will help improve the management of these patients.

Table of Contents

1. Introduction and literature review

In 2012, diabetes mellitus (DM) was the cause of death of an estimated 4.8 million people. Worldwide, diabetes is responsible for 8.2% of all deaths, and half of the people who die from diabetes are under the age of 60.[1] Previously, DM was considered a rare condition in sub-Saharan Africa.[2,3] However, today, Africa is the hardest hit region in terms of diabetes-related mortality.[1] Mortality attributable to diabetes in sub-Saharan Africa was estimated in 2010 at 6% of total mortality - an increase from 2.2% to 2.5% from 2000.[2]

Overall, more than 371 million people have diabetes according to the latest release of the International Diabetes Federation (IDF) Diabetes Atlas.[1] There has been an increase in the number of people with type 2 diabetes (T2DM) in every country. Furthermore, four out of five people with diabetes live in low- and middle-income countries.[1] Figure 1 shows the global estimates of the number of people with diabetes worldwide according to IDF.



REGION	2011 MILLIONS	2030 MILLIONS	INCREASE %
Africa	14.7	28.0	90%
Middle East and North Africa	32.8	59.7	83%
South-East Asia	71.4	120.9	69%
South and Central America	25.1	39.9	59%
Western Pacific	131.9	187.9	42%
North America and Caribbean	37.7	51.2	36%
Europe	52.6	64.0	22%
World	**366.2**	**551.8**	**51%**

Figure 1: Projections of the number of people with diabetes (20 - 79 years), 2011 and 2030.[1]

In Africa, the increase of the prevalence of diabetes is the result of factors such as population ageing and lifestyle changes associated with rapid urbanisation and

westernisation.[2-5] According to IDF estimates in 2009, there will be a 98% increase in the number of adults with DM on the African continent, between 12.1 million in 2010 and 23.9 million in 2030.[2] T2DM is the predominant form (70% to 90%) of DM in Africa.[2-5] Finally, African diabetes is associated with a high complication burden, compared to developed countries.[2,3]

1.1. Definitions

DM comprises a heterogeneous group of metabolic diseases that are characterised by chronic hyperglycaemia and disturbances in carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion and/or insulin action. Hyperglycaemia is largely responsible for the acute, short-term, and late complications that affect all body organs and systems.[6]

The aetiological types of DM include type 1, type 2, other specific types and gestational diabetes. The requirement of insulin treatment is no longer used as a means to classify diabetes since patients with any form of diabetes may require insulin treatment at some stage of their disease. Type 1 diabetes mellitus (T1DM), which accounts for only 5% to 10% of cases, results from pancreatic beta-cell destruction. These patients are prone to ketoacidosis, coma and death. T2DM is the most common type (> 90% of cases) and is predominated by disorders of insulin action (insulin resistance), with insulin deficiency relative to demand (i.e. disorders of insulin action and secretion).[7]

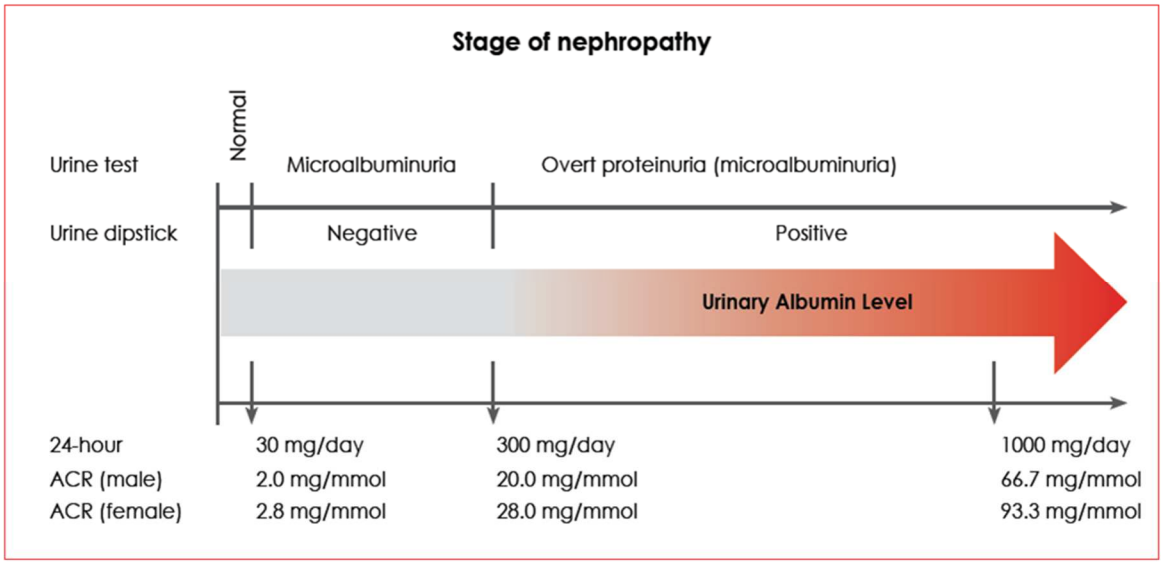
DM complications include macrovascular disease, leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, and microvascular damage causing diabetic retinopathy and diabetic nephropathy (DN), and contributing to diabetic neuropathy.[8]

1.2. Diabetic nephropathy

DN also known as Kimmelstiel Wilson syndrome, was first discovered in 1936 by Clifford Wilson and Paul Kimmelstiel who described the classic lesions of nodular glomerulosclerosis associated with proteinuria and hypertension.[9,10]

DN is both the major cause of end-stage renal disease (ESRD) in developed countries (~30% of cases)[6,9-14], as well as the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy (RRT).[15] In the near future, DN is expected to be the most frequent cause of ESRD in the developing world.[12] About 20% to 30% of people with T1DM and T2DM develop DN, and the incidence increases with duration of diabetes.[6] Elsewhere, it has been reported that up to 35% of all patients with either T1DM or T2DM eventually develop nephropathy after 25 to 30 years of diabetes.[16] However, certain ethnic and racial groups demonstrate high prevalence rates of severe nephropathy (Native Americans, Mexican Americans, and African Americans).[6,14]

DN is a clinical syndrome characterised by persistent albuminuria (>300mg/24hr), a relentless decline in glomerular filtration rate (GFR), and hypertension. Nephropathy is rare during the first five years of diabetes, increasing to a peak at 15 to 20 years after the onset of disease. Microalbuminuria (>30mg/day and <300mg/day), the earliest clinical evidence of kidney damage, strongly predicts the development of DN and is associated with increased cardiovascular mortality.[17] The stages of classic DN are illustrated in Figure 2, including diagnostic methods.



ACR = urinary albumin: creatinine ratio

Figure 2: Stages of diabetic nephropathy with diagnostic methods.[18]

The cut-off values adopted by the American Diabetes Association (ADA) are 30 to 299 mg/g for microalbuminuria and >300 mg/g for macroalbuminuria measured on a spot urine sample.[15]

Table I and Table II present the clinical stages of DN according to the GFR and to urine albumin-to-creatinine ratio (ACR) respectively.

Table I: Clinical stages of diabetic nephropathy[16]

STAGE	GFR*	UAE≠ (mg/day)	BLOOD PRESSURE	YEARS AFTER DIAGNOSIS
I. Hyperfiltration	Supernormal	<30	Normal	0
II. Microalbumineria	High-normal to normal	30-300	Rising	5-15
III. Proteinuria	Normal to decreasing	>300	Elevated	10-20
IV. Progressive nephropathy	Decreasing	Increasing	Elevated	15-25
V. ESRD#	<15 mL/min	Massive	Elevated	20-30

#: end-stage renal disease; *: glomerular filtration rate; ≠:urinary albumin excretion

Table II: Stages of classic diabetic nephropathy according to urinary albumin level[18]

Stage	Urine dipstick for protein	Urine ACR (mg/mmol)		24- urine collection for albumin (mg/day) (mg/day)
		Men	Women	
Normal	Negative	<2.0	<2.8	<30
Micro-albuminuria	Negative	2.0-20.0	2.8-28.0	30-300
Overt nephropathy (macroalbuminuria)	Positive	>20.0	>28.0	>300
		>66.7	>93.3	>1000

1.2.1. Screening for diabetic nephropathy

The ADA and the Canadian Diabetes Association (CDA), as well as the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) recommend that screening must be initiated at the time of diagnosis in patients with T2DM, and at 5 years after diagnosis for T1DM patients. If microalbuminuria is absent, the screening must be repeated annually for both T1DM and T2DM.[7,15,18,19]

The first step in the screening and diagnosis of DN is to measure albumin in a spot urine specimen, collected either as the first morning urine or at random; for example, during a medical visit.[11,15,20] This method is accurate, easy to perform, and recommended by the ADA guidelines.[15]

Twenty-four–hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time; therefore, they are not recommended in routine clinical pratice.[15,19,21]

The results of albumin measurements in spot collections may be expressed as urinary albumin concentration (mg/l) or as urine ACR (mg/g or mg/mmol).[15] A urine ACR of 2.0mg/mmol in men and 2.8mg/mmol in women (30mg/g in sex) or higher suggests presence of microalbuminuria.[18,22] Because of variability in urinary albumin excretion (UAE), two of three specimens should be abnormal before the diagnosis of DN is made.[7,15,18,19]

Screening should not be performed in the presence of conditions that increase UAE. Such conditions include urinary tract infection, haematuria, acute febrile illness, vigorous exercise, menstruation, pregnancy, acute severe elevations of blood pressure or blood glucose, and uncontrolled heart failure.[7,15,18,23]

The following are alternatives when specific UAE measurements are not available:

- Semi quantitative dipstick measurements of albuminuria (e.g. Micral Test II); and
- A qualitative test for proteinuria (dipstick), or a quantitative measurement of protein in a spot urine sample.[15]

1.2.2. Assessment of renal function

Once the diagnosis of DN is made, the renal function must be assessed in order to measure the progression of DN or eventually to confirm the need for treatment of ESRD.[24]

The measurement of glomerular filtration rate (GFR) is accepted as the best overall measure of kidney function.[15,21] The renal clearance of inulin during constant infusion has been considered the gold standard for determination of GFR.[25] However, this method is not used because the procedures are cumbersome, and also because of the cost and limited availability of inulin.[24]

1.2.2.1. Measurement of GFR

GFR is measured as the urinary or plasma clearance of an ideal filtration marker such as inulin. However, because of the reasons mentioned above, other markers are preferred for the measure of GFR.

Serum creatinine is the most frequently used measure of kidney function in clinical practice because of low cost and little inconvenience for the patient; however, the creatinine may falsely indicate that a person's renal function is normal.[18,24] In fact, the generation of creatinine also depends on muscle mass and dietary intake of protein. It should also be noted that some drugs, including trimethoprim, cimetidine, salicylates, triamterene and amiloride, may interfere with creatinine excretion and cause a false elevation in the serum creatinine value.[21,22,24] The use of serum creatinine is recommended by the ADA, as well as by the SEMDSA.

1.2.2.2. Estimation of GFR

In clinical practice, the estimated GFR or eGFR can be calculated to evaluate kidney function, using equations that take into account serum creatinine concentration and some or all of the following variables: age, sex, race, and body size. The two preferred methods are: the Cockcroft–Gault formula and the Modification of Diet in Renal Disease (MDRD) study equation.[11,15,21,24,25]

The Cockcroft–Gault formula was developed in 1973. This method estimates creatinine clearance, which is known to overestimate GFR because of the tubular secretion of creatinine.[25] The values are not adjusted for body-surface area; a comparison with normal values for creatinine clearance requires measurement of height, computation of body-surface area, and adjustment to 1.73 m^2.[24]

The Modification of Diet in Renal Disease (MDRD) study equation was developed in 1999.[21] The equation estimates GFR adjusted for body-surface area. GFR is expressed in millilitres per minute per 1.73 m^2, and race is either black or not; the MDRD formula is more accurate than either the use of the Cockcroft–Gault formula or the measurement of creatinine clearance.[21,24] The MDRD formula is now considered state of the art for routine clinical estimation of renal function.[25]

In some studies, the MDRD study equation has been reported to be more accurate than the Cockcroft-Gault formula, in contrast other studies have found that they produce similar results.[21] The Cockcroft-Gault formula appears to be less accurate than the MDRD study equation in older and obese people,[21] whereas the MDRD equation accounts for the biological differences in creatinine metabolism observed in black patients compared to white patients.[25]

The classification of CKD according to the eGFR is presented in Table III.

Table III: Stages of CKD according to eGFR[18]

Stage	Qualitative description	eGFR (mL/min)
1	Kidney damage, normal GFR	≥90
2	Kidney damage, mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	End-stage renal disease	<15 (or dialysis)

1.2.3. Risk factors

1.2.3.1. Factors that accelerate DN progression

Numerous studies have demonstrated the influence of a variety of modifiable and non-modifiable factors on the development and progression of nephropathy in diabetic patients.

- Non-modifiable factors:

- Genetic susceptibility: Epidemiological and familial studies have demonstrated that genetic susceptibility contributes to the development of DN in both T1DM and T2DM patients.[11,15] The familial clustering of DN has been described,[26] and several studies have shown an association between a family history of ESRD and increased risk of ESRD.[27,28]
- Race: Incidence and severity of DN are increased in blacks, Mexicans Americans, Pima Indians, and Hispanics compared with Caucasians;[27-29]
- Male gender;[26,29] and
- Advanced age.[26]

- Modifiable factors:

Potentially modifiable DN initiation and progression risk factors in susceptible individuals are sustained hyperglycaemia and hypertension, glomerular hyperfiltration, obesity, proteinuria level, dietary factors such as the amount and source of protein and fat in the diet.[11,15,28]

Smoking: patients with T2DM who smoke have a greater risk of microalbuminuria than patients who do not smoke, and their rate of progression to ESRD is about twice as rapid.[11,15,26,29]

Dyslipidaemia: studies have suggested that lipids may play a role in the development and progression of DN. [11,15,26,29]

1.2.3.2. Factors that slow DN progression

The following interventions have been proven effective in slowing progression of DN:

- Normalisation of glycaemia;
- Strict blood pressure control; and
- Administration of Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs). Dyslipidaemia should also be treated.[30]

Table IV provides a summary of the management of diabetic patients with nephropathy.

Table IV: Strategies and goals for reno- and cardioprotection in patients with diabetic nephropathy[15]

	Goal	
Intervention	Microalbuminuric	Macroalbuminuric
ACE inhibitor and/or ARB and low-protein diet (0.6–0.8 g · kg wt^{1} · day1)	Reduction of albuminuria or reversion to normoalbuminuria	Proteinuria as low as possible or <0.5 g/24-h
	GFR stabilisation	GFR decline <2 ml · min^{1} · year^{1}
Antihypertensive agents	Blood pressure <130/80 or 125/75 mmHg	
Strict glycaemic control	A1c <7%	
Statins	LDL cholesterol <100 mg/dl	
Acetyl salicylic acid	Thrombosis prevention	
Smoking cessation	Prevention of atherosclerosis progression	

A strict and meticulous control of hypertension slows the rate of decline in GFR. Blood pressure should be maintained under 130/80 mmHg. ACE inhibitors have a marked antiproteinuric effect and are used in patients with either incipient or overt DN or in patients with microalbuminuria, even if normotensive.

Control of blood glucose: excellent glycaemic control reduces the risk of kidney disease and its progression in both T1DM and T2DM. It is recommended that plasma values for pre-prandial glucose be kept in the 5.0 to 7.2 mmol/L (90 to 130 mg/dL) range and haemoglobin A1C (HbA1C) should be < 7%.[31]

Control of blood pressure and proteinuria: microalbuminuria precedes the decline in GFR and announces renal and cardiovascular complications. Antihypertensive treatment reduces albuminuria and diminishes its progression even in normotensive diabetic patients. In addition to treatment for hypertension in general, the use of ACE inhibitors and ARBs is associated with additional renoprotection.[31]

1.3. Diabetic nephropathy in Africa

DN is the leading cause of ESRD for all Americans, accounting for nearly 45% of new cases each year. Among all racial groups, African Americans have the second highest rate of diabetes-related ESRD.[6,32] In the United States of America, DN is more prevalent among African Americans, Asians and Native Americans than Caucasians.[15]

In Africa, microvascular complications, including DN, are highly prevalent because of poor levels of glycaemic and blood pressure control; complications are found early in the course of the disease as diagnosis of diabetes mellitus is often delayed.[5]

DM contributes to a third of all patients admitted to dialysis units in Africa.[33] Unfortunately, dialysis and renal transplantation therapy are almost completely inaccessible to African diabetic patients.[5] Consequently, diabetic end-stage renal failure is the most frequent cause of hospital mortality in diabetic patients in Africa.[33] According to a study conducted in South Africa and published in 2004, renal failure was a major cause of death among a population of T2DM patients (29%).[34]

The prevalence of nephropathy varies between 32% to 57% after a mean duration of diabetes of 5 to 10 years, and 5% to 28% within the first year following the diagnosis of diabetes.[3,33] Overt proteinuria is found in 5% to 28% of the patients, and increases with diabetes duration. However, there is no great difference in the prevalence of nephropathy between T1DM and T2DM patients.[33] The prevalence is estimated to be 14% to 16% in South Africa, 23.8% in Zambia, 12.4% in Egypt, 9% in Sudan, and 6.1% in Ethiopia.[35]

There is a dearth of published studies focusing on DN and its evolution in sub-Saharan Africa. Most of the available data on DN in Blacks come from studies conducted among African-American patients in the USA.[27,28,36,37] As a result, the relationship between DN and good or bad diabetes management in black Africans are not well understood.

Studies have been conducted in Cameroon,[38] Kenya,[39] Tanzania,[40] and Ethiopia.[41] They were for the most part prevalence (cross-sectional) studies, except from the Ethiopian study which was a prospective cohort study over a 6-week period that aimed at assessing the glycaemic control and burden of complications including nephropathy in a group of diabetic patients.[41] A 12-year follow-up study conducted in South Africa considered the renal outcome in diabetic patients, but only T2DM patients were included and the sample was relatively small (59 patients, 9 of whom were black).[34]

Therefore, the proposed study, an analytical cross-sectional study focusing on black African diabetic patients, will provide useful information on DN in our settings.

2. Aim and objectives

2.1. Aim

The aim of the proposed study is to examine the relationship between diabetes control parameters (HbA1C, blood pressure level and lipids) and DN in African patients with diabetes.

2.2. Study objectives

In diabetic patients:

1) To determine the point prevalence of DN;
2) To determine the proportions of patients controlled regarding blood pressure, HbA1C and lipids.
3) To determine association if any between (2) and (1).

3. Methods

3.1. Study design

The proposed study will be an analytical cross-sectional study design.

3.2. Study setting

The proposed study will utilise secondary data collected in 2012 from the Kalafong Diabetes Clinic.

Kalafong Hospital is a tertiary public hospital in Pretoria, Gauteng province (South Africa). The hospital is situated on the Western outskirts of Pretoria in the suburb of Atteridgeville. The University of Pretoria uses the hospital as a training site for the Faculty of Health Sciences.

The Kalafong Diabetes Clinic operates on Wednesdays and Fridays. Patients seen at the clinic are usually referred on the basis of two criteria: either diabetes or blood pressure difficult to control; or presence of diabetes complications. An average of 800 diabetic patients is followed up every year at the clinic. Every patient is entitled to a minimum of four visits per year (every three months). Each of the four visits has a specific focus: the first visit is the foot visit, the second visit is the cardiovascular visit, the third visit is the eye visit, and the fourth visit is the general visit.

Kidney function is assessed twice a year with a serum Creatinine and urine ACR.

3.3. Study population and sampling

3.3.1. Study population

The study population for the proposed study will be diabetic patients who were seen at the Kalafong diabetic clinic in 2012.

Exclusion criteria

- All patients with nephropathy due to other causes; and
- Patients younger than 18 years old.

3.3.2. Sampling method and sampling size

A point prevalence of diabetic nephropathy in this population is expected to be between 5% and 10%. Assuming the finite population of between 700 and 800 patients the minimum sample size required with a 5% margin of error is calculated to be 248. However we have the data for the whole population of 700 to 800 patients who attended the clinic in 2012, therefore the whole population of patients on the diabetic clinic database will be used, thus no sampling employed.

3.4. Measurements

At each visit, the following are measured: serum glucose, arterial blood pressure, and weight. A urine dipstick is also done. Arterial blood pressure is measured using Vital Signs Monitor Mindray VS-800 (Mindray Shenzhen). Serum glucose is

measured using Accu Check Active (Roche Manheim). Makromed Urine Test Strips are used for urinalysis (U-dipstix).

The following measurements are performed in the laboratory:

- Urine;
- Serum glucose, using GLUC (Dimension® clinical chemistry system, Siemens);
- Haemoglobin A1C concentration, using HB1C assay (Dimension® clinical chemistry system, Siemens);
- Serum creatinine and urine ACR is expressed in mg/mmol.

Exposure variables

They will include demographics (race, gender, age, height, and weight), type of diabetes, and duration of diabetes.

Diabetes control parameters: HbA1C, blood pressure and lipids.

Poor glucose control will be defined as HbA1C >7%.

Poor blood pressure control will be defined as blood pressure >130/80 mmHg.

Poor lipids control will be defined as triglycerides >1.7 mmol/L or LDL cholesterol >1.8 mmol/L.

Outcome variables

The following will be outcome variables:

Continuous: serum creatinine, urine ACR

Ordinal: urine protein on dipstix

Binary: microalbuminuria, macroalbuminuria, low eGFR.

DN will be defined as microalbuminuria (2.0 mg/mmol < urine ACR < 28 mg/mmol) or macroalbuminuria (urine ACR ≥28 mg/mmol).

4. Data management and analysis

Data will be anonymous and patients will be identified through the hospital identification number only.

No patient files will be required because all the patient data are routinely captured in the Kalafong diabetes clinic database. Appropriate data will be extracted from the electronic database of the Kalafong Diabetes Clinic with permission from the custodian of the data (the CEO of Kalafong Hospital). The Kalafong Diabetes Clinic database is a Microsoft Access database. A query will be run on the database to extract the relevant information and this data will be exported to a Microsoft Excel file, which will be used in the analysis.

Statistical analysis

Descriptive statistics will be done for all variables with appropriate methods based on the type of data and the distribution of the data.

Frequency tables, cross tabulation and Chi square tests will be used. Logistic regression will be performed.

All data analysis will be done in SPSS and STATA.

Data storage

All data will be stored in electronic format on a dedicated hard drive utilised by Internal Medicine only on the Klinikala server. A copy of the data will also be stored on an Internet-based storage facility (Dropbox). All data will be password protected.

5. Ethical and legal considerations

Approval to conduct the proposed study will be sought from the Academic Programme Committee of the School of Health Systems and Public Health and the Student Ethics Committee of the Faculty of Health Sciences.

As a routine practice, all patients enrolled at the Kalafong Diabetes Clinic are requested permission to use routinely collected clinical information for research purposes. However, this is not formal informed consent. Therefore, the permission to use routinely collected patient information will be obtained from the custodian of the data (the CEO of Kalafong Hospital).

All patient information will be kept strictly confidential. The extracted dataset from the database will contain only hospital numbers, and no other means of identification. Once the information is extracted from the database, no one will be able to identify the participants. Research reports and articles in scientific journals that are based on the results of the study will not include information that may identify participants. Because of the use of secondary data, there are no additional risks to participants in this study.

Participants will not directly benefit from participating in this study, but diabetic patients similar to the study population may benefit from the results of the proposed study if it leads to change in the management of such patients.

6. Logistics and time schedule

GANTT CHART

(From January 2013 to December 2013)

ACTIONS	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Literature study												
Protocol writing												
Statistician consultation												
TNM 800 course												
Ethical aspects												
Data processing												
Statistical analysis												
Report writing												
Publication preparation												
Congresses												

Authorship and contributors

Name	Department	Contribution	Author or acknowledgement
P. Ngassa Piotie	SHSPH	Researcher	Author
D.G. van Zyl	Department of Internal Medicine, University of Pretoria	Supervisor	Second author
P. Rheeder	SHSPH	Co-supervisor	Third author

7. Budget/Resources

Item description	Budget
Transport	R1200
Computer	R4000
Printer	R1500
Data cleaning	R500
Printing of MPH research report	R200
Publication costs	R2000
Total	**R9400**

The proposed study do not benefit from any grant or sponsor, therefore the investigator will bear all costs related to the study.

The study will not incur additional cost to Kalafong Hospital above that of standard care routinely delivered at the Diabetes Clinic.

8. Reporting of results

The purpose of this study is to write a research report as a requirement for an MPH and to have the study and its results published in a peer-reviewed journal.

9. References

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10. Appendices

-Letters of approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 13/04/2011 and Expires 13/04/2014.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

12/06/2013

Approval Notice
New Application

Ethics Reference No.: 154/2013

Title: Diabetic nephropathy and its associations with diabetes control parameters in a tertiary care diabetes clinic
Dept:SHSPH Department/ Hospital/Institution: University of Pretoria. **Cell:** 0798484101 **E-Mail:** patoungassa@yahoo.fr **Hash**#: 10385020 (student number)

Dear Dr Patrick NGASSA PIOTIE

The **New Application** for your research received on the 07 May 2013, was approved by the Faculty of Health Sciences Research Ethics Committee on the 29 May 2013.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year, till the end of November 2013.
- Please remember to use your protocol number (**154/2013**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
Standard Conditions:

- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

We wish you the best with your research.

Yours sincerely

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