PROGRESSION OF MICROALBUMINURIA AMONG DIABETIC PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA OVER A NINE YEAR PERIOD.

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By

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A dissertation submitted in (Partial) Fulfillment of the Requirements for the Degree of Masters of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences
October, 2013

CERTIFICATION

The undersigned certify that she has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Scienc**es** a dissertation entitled ***''Progression of Microalbuminuria Among Diabetic Patients Attending MNH Over A Nine Year Period''*** in fulfillment of the requirements for the degree of Masters of Medicine (Internal Medicine) of Muhimbili University of Health and Allied sciences.

_____

Prof: J. Lutale

Supervisor

_____

Date

DECLARATION AND COPYRIGHT

I **Dr. Yona Gandye** declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…….. **Date**.....

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Thanks.

DEDICATION

This dissertation is dedicated to my mother Suzana Maliva who motivated and ensured I go to school all the way from primary to university.

ABSTRACT

Background

Microalbuminuria presents with different degrees of progression as it may regress to normoalbuminuria or progress to the irreversible stage of diabetic nephropathy and eventually end stage renal disease. Most available information are reports of studies done among Caucasians and there is paucity of such evidence among diabetic African patients describing the progression of microalbuminuria**.** This study aimed at determining the progression of microalbuminuria in patients with diabetes over a nine year period at MNH.

Methods

A retrospective cohort study involved 259 participants a cohort of type 1 and type 2 diabetic patients who participated in the baseline study in 2003/2004. Urine samples were first screened using dipstick strip from the spot morning void urine. Patients who had dipstick negative for albuminuria were further tested using a semi-quantitative assay to determine albuminuria and creatinine concentrations in order to calculate ACR. Further information obtained included age, diabetes duration, sex, body mass index, blood pressure, serum lipid profile, serum creatinine and glycated haemoglobin.

Results

High proportion of patients with microalbuminuria progression occurred in type 2 diabetes (83.3%) whereas half of the patients with diabetes type 1 presented with microalbuminuria persistence. Risk factor assessment showed that diabetic duration of 10-15yrs, poor glycemic control especially HbA1C >10%, isolated diastolic and both systolic and diastolic hypertension were associated with microalbuminuria progression.

Conclusion

This study aimed at assessing the progression of microalbuminuria among diabetic patients over nine years at MNH diabetic clinic. The main finding of the study was high rate of microalbuminuria progression which occurred among the diabetic patients. Among the 74 patients with normoalbuminuria at the baseline who could be traced 93.2% of them their albuminuria progressed either to microalbuminuria 37 (50%), or progressed to macroalbuminuria 32 (43.2%). Whereas among those patients who had microalbuminuria at baseline, 75% progressed to macroalbuminuria and 25% persisted as microalbuminuria, none of them regressed towards normoalbuminuria. Additionally we found that progression of albuminuria occurred in both diabetic groups, the majority of progressers (83%) were observed among type 2 diabetic patients. This progression occurred mainly among diabetic patients with diabetic duration 10-15yrs, poor glycemic control (HbA1C >10%) and diastolic or both systolic and diastolic hypertension.

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ABBREVIATIONS:

CVA	-	Cardiovascular Accident
MA	-	Microalbuminuria
GFR	-	Glomerular filtration rate
DN	-	Diabetic nephropathy
HBA1C	-	Glycosylated hemoglobin
AER	-	Albumin excretion rate
UK	-	United Kingdom
ACE	-	Angiotensin converting inhibitor
BMI	-	Body mass index
WT	-	Weight
CL_{cr}	-	Creatinine clearance
ACR	-	Albumin excretion rate
MNH	-	Muhimbili National Hospital
US	-	United States
MICRO	-	Microalbuminuria, cardiovascular, and renal outcomes
HOPE	-	Heart outcome prevention evaluation
NIDDM	-	Non insulin depended diabetic mellitus
ARBs	-	Angiotensin receptor blockers
TRIG	-	Triglycerides
LDL	-	Low density lipoprotein
CHOL	-	Cholesterol
GFR	-	Glomerular filtration rate

DEFINITION OF TERMS

Progression- Advancing deterioration in renal functioning as reflected by worsened albuminuria status as compared to the baseline status.

Regression- Improvement in renal dysfunction status as reflected by reduction in albuminuria as compared to the baseline status.

Persistence- Albuminuria status that does not worsen (progress) or improve (regress) with time as compared to the baseline status.

End stage renal failure- Was defined as GFR< 15ml/min.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

PROGRESSION OF MICROALBUMINURIA

Diabetic patients with microalbuminuria have increased risk of progression to overt proteinuria, and after some time, renal failure. Studies have shown that microalbuminuria may spontaneously resolve to normoalbuminuria in a substantial proportion of patients, mainly in type 1 diabetics, or may progress to macroalbuminuria referred to as overt nephropathy [1,2]

It has been reported that without intervention, approximately 80% Type 1 patients with persistent microalbuminuria would develop overt nephropathy after a period of 10–15 years where as 50% of these develop end stage renal failure within 10 years and 75% by 20 years [3,4]

In Type 2 diabetic patients it has been found that 20–40% of these patients with microalbuminuria would progress to overt nephropathy over the same period of 10-15 years and 20 years later, approximately 20% develop end stage renal failure. It has been reported that the progression of diabetic nephropathy from the appearance of overt proteinuria to end stage renal failure is usually irreversible[5]. The rate of progression to diabetic nephropathy in affected people with Type 2 diabetes have been reported to be 5% per year and 7.5% per year in Type 1 diabetes[6]

In a study done by Bahman et al 2001 at Michigan, USA among type 1and type 2 diabetic patients with microalbuminuria to determine the outcome of microalbuminuria, showed that among patients (Type 1 and 2) with persistent MA at baseline only 6% of them progressed to overt diabetic nephropathy over a 7-yr follow up period. About 38% did not progress while 56% regressed to normoalbuminuria. [7]

Moreover several risk factors associated with progression of microalbumnuria to diabetic nephropathy have been identified among type 1 and type 2 diabetics, these include longer duration of diabetes, hyperglycemia, hypertension, dyslipidemia, cigarette smoking, and family history of hypertension.[8-13]

Level of glycaemic control and albuminuria progression

Hyperglycemia has been reported to affect the rate of progression of microalbuminuria in diabetic patients. The risk of progression to proteinuria among microalbuminuric patients has been found to be influenced by the level of glycemic control where by diabetic patients with poor glycemic control have tendency toward fast progression.

A 4yr follow up study among type 1 diabetic patients in US.(Warram JH et al 2000)[14] showed that improved glycemic control at HbA1c level of less than 8.5% was associated with reduced progression to overt proteinuria. In this study the incidence rate varied significantly depending on the level of glycemic control. When $HbA1_C$ was maintained < 8.0% the incidence rate of progression was low (1.3 per 100 person-years), when HbA1c increased so were the incidence rates of progression: it was found that HbA1c 8.0-8.9% had incidence rate of progression of 5.1 per 100 person years, HbA1c 9.0-9.9% incidence rate of progression of 4.2 per 100 person years and HbA1c 10.0-13.1% incidence rate of progression of 6.7 per 100 person-years. The risk of progression rose steeply between an HbA1c of 7.5-8.5% and then remains approximately constant across higher levels (a non linear dose response relationship).

Another study was done in USA (Ficociello LH 2007)[15]to determine the risk factors associated with progression of microalbuminuria to proteinuria among type 1 diabetes and found that poor glycemic control was among the major determinants/predictors associated with MA progression.

Blood pressure control and albuminuria progression

Arterial hypertension has been found to be a main risk factor for progression of microalbuminuria and the development of DN[16], and probably the best known relevant factor related to its progression.

It has been found that for every 10 mmHg drop in systolic BP there is 13% reduction in the risk of microvascular complications, with significantly lowered risk in patients with systolic BP maintained at <120 mm Hg according to UKPDS 2000 by Amanda I. Andler et al [17]a

prospective study aimed at determining the association of systolic blood pressure with macrovascular and microvascular complications among type 2 diabetes patients.

A similar study was done in US involving three follow-up periods to determine the regression of microalbuminuria in 386 diabetic type 1 participants with persistent microalbuminuria; it was found that lowering systolic blood pressure was associated with significant regression of microalbuminuria in these patients.[18]

Furthermore a study [19]conducted by James H et al in 1999 showed that the risk of progression to proteinuria among microalbuminuric patients was influenced by the level of diastolic blood pressure with the dose response relationship being linear for diastolic blood pressure.

Dyslipidemia and microalbuminuria progression.

Several studies have shown that MA progression is associated with increased serum total cholesterol and reduced serum HDL cholesterol[20, 21] whereby the most consistent finding was the presence of lower levels of HDL pausing a risk of microalbuminuria progression. And it was furthermore suggested that clearance of LDL cholesterol was an important physiological process as lower levels of this lipoprotein are associated with less cellular injury that leads to microvascular complication causing microalbuminuria progression.[22]

In 1997 Simulders YM et.al[23] conducted a study in Netherland to identify the determinants of progression of microalbuminuria in patients with NIDDM. They showed that in these patients with NIDDM dyslipidemia was a strong predictor of more rapid progression of microalbuminuria despite a well-controlled blood pressure.

Another similar study was done in US (Bruce A. et al 2003)[18] involving 386 participants with diabetes type 1and persistent microalbuminuria in order to determine the regression of microalbuminuria, in this study it was showed that low level of either cholesterol or triglycerides alone approximately doubled the chance of the regression of microalbuminuria.

Smoking and microalbuminuria

Cigarette smoking especially when accompanies poor glycemic control has been considered to be a risk factor for diabetic nephropathy particularly in type 1 diabetes. However, the association to the onset of this complication is said to be not yet established.

Patients with type 1 diabetes who smoke with their HbA_{1c} maintained >8% have the highest risk of onset of microalbuminuria with incidence rate of 3.3/100 person-years by Laura J. et..al 2001 in US involving 943 patients on a nonlinear effect of hyperglycemia and current cigarette smoking on a 4yr follow up study.[24]

In synergistic way smoking has been found to cause both poor glycaemic control and microalbuminuria in patients with diabetes independently of other characteristics in a study done in Sweden aimed at determining the association between smoking, glycaemic control and microalbuminuria by P M Nilsson et.al 2001[25]

However despite the evidence that smoking combined with poor glycemic control affected the onset of MA as shown above there is no existing information showing the role of smoking on the progression of microalbuminuria to overt diabetic nephropathy.

Family history and microalbuminuria progression

It has been reported that in families with two or more siblings with type 1 diabetes, when one sibling has developed nephropathy, the other has a fourfold risk of nephropathy compared with a sibling of a patient without nephropathy

In US it was shown that probands and si**b**lings had increased combined cumulative incidence of developing advanced diabetic nephropathy up to 35% after 30 yrs of type 1 diabetes by Quinn M et al 1996 (Familial factors determine the development of diabetic nephropathy in patients with IDDM).[**26**]

Diabetic duration and microalbuminuria progression

It has been documented that, in diabetes persistent microalbuminuria is predictor of development of overt diabetic nephropathy, progressive renal insufficiency and increased risk of cardiovascular disease, in both type 1 and 2 diabetes[27, 28]. Approximately 30% of type 1 diabetic patients may develop diabetic nephropathy within 25 years of diabetes although evidence have suggested a declining incidence[29]

A study by Peter Rossing et al 2005 in Denmark in a ten-year prospective observational study aimed to determine the progression of microalbuminuria in type 1 diabetes found that longer duration of microalbuminuria (persistent microalbuminuria) in diabetic patients had close association with high risk for progression of microalbuminuria to overt proteinuria [30]

Similarly, in 2003 another study was done in USA (Chankramath S. Arun et al) [31] to determine the significance of long-duration in type 1 diabetes with microalbuminuria where it was found that MA is a good predictor of persistent proteinuria in patients with long-standing type 1 diabetes of >30 years' duration .

Antihypertensive drugs and progression of MA

It has been reported that there are both renal and cardiovascular protective effects of lowering microalbuminuria in diabetic patients when using antihypertensive regimens containing angiotensin converting enzyme (ACE)-inhibitors, angiotensin receptor antagonists, or non-dihydropyridine calcium channel blockers. Based on this intervention, it has been noted that there is a significant increase in the median life expectancy in type 1 diabetics, with mortality reduction (94 to 45%) associated with progression to overt nephropathy. Therefore lowering blood pressure with ACE inhibitor or angiotensin receptor blocker as a part of the antihypertensive cocktail in patients with microalbuminuria appears to be crucial to both normotensive and hypertensive diabetic patients.[6]

In 2007, Barry M et…al conducted a REENAL study to determine the renal protective benefits of losartan involving 1513 participants with diabetes and nephropathy, it was shown that Losartan conferred significant renal protection among these patients with 28% risk reduction towards ESRD progression[32]

Similarly, it has been shown that progression of baseline microalbuminuria to overt nephropathy was lowered by 24% with ramipril intervention in a (MICRO) HOPE study (Argentina et.al 1998) in a long term clinical trial involving 3577 participants with diabetes in Canada[33]

DIABETES AND DIABETIC NEPHROPATHY

Development of kidney complications, known as diabetic nephropathy, consists of several stages: the onset of microalbuminuria, its progression to overt proteinuria, and progression of the proteinuria to end-stage renal disease [34,35]Microalbuminuria (MA) is the first sign of incipient nephropathy and other micro vascular complications in this diabetic population. It is considered to be a risk factor for diabetic nephropathy (DN) and progressive renal insufficiency in diabetes characterized by a progressive increase in proteinuria and decline in GFR, hypertension and a high risk of cardiovascular morbidity and mortality. [8, 36,37,38,39] Therefore, microalbuminuria essentially predicts worsening of renal disease to overt diabetic nephropathy [40] and an elevated risk of cardiovascular disease [41,42,43,44.]

Diabetic nephropathy accounts for a significant reduction in life expectancy of diabetic patients and is a leading cause of end-stage renal disease in the western world. [45,46.] It is a common complication of diabetes as nearly 50% of diabetic patients with more than 20 yrs of diabetes have a higher percentage of progression to ESRD with the majority being TIDM. Up to 30% of people with newly diagnosed type 2 diabetes will already have abnormally high urine albumin levels, about 75% of these people will have microalbuminuria and about 25% will have overt diabetic nephropathy. Therefore higher proportion of individuals with type 2 diabetes was found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes. This is because diabetes is actually present for many years before the diagnosis is made. [48]

EPIDEMIOLOGY

The prevalence of diabetic nephropathy and end stage renal failure has been found to be higher among African Americans patients; this is mainly due to high prevalence of diabetes among blacks. [49, 44]

It is estimated that approximate 7.0% of the total population U.S are diabetic with growing incidence with diabetes appearing to be a main cause of end stage diabetic renal disease [50, 51]It is extrapolated that the number of adults living with diabetes worldwide will rise from 135 million in 1995 to 300 million in the year 2025 due this growing burden of diabetes.[54]

The prevalence of MA was reported to be 28.8% in 22,244 participants aged 6yrs and older with previously diagnosed diabetes in a US population by Rahlenbeck SI et.al. [51]

A crossectional study done in Gondar, Ethiopia involving diabetic outpatients estimated the prevalence of micro and macroalbuminuria to be 32% and 15% in IDDM patients while for NIDDM this was approximately 37% and 20% respectively by Sibylle et.al 1995. [5]

STATEMENT OF THE PROBLEM

Microalbuminuria is considered to be a risk factor for Diabetic nephropathy and progressive renal insufficiency in diabetic patients. [8, 36,37,38,39] Diabetic patients with microalbuminuria have been documented to have increased risk of progression to overt proteinuria, and after some time, renal failure which accounts for significant reduction in life expectancy. It is a leading cause of end-stage renal disease in developed countries. [45, 46]

It has been reported that without intervention, approximately 80% Type 1 patients with persistent microalbuminuria would develop overt nephropathy after a period of 10–15 years where as 50% of them develop end stage renal failure within 10 years and 75% by 20 years [3, 4]. In Type 2 diabetic patients, it has been found that 20–40% of these patients with microalbuminuria would progress to overt nephropathy and 20 years later, approximately 20% will have developed end stage renal failure[5].With this progression of microalbuminuria, patients with diabetes are at an increased risk of developing chronic kidney disease with an excess cardiovascular mortality.

Early detection of microalbuminuria with appropriate intervention delays or halts progression to an irreversible stage of diabetic nephropathy and end stage renal failure. Several epidemiological studies report constantly high association of microalbuminuria and the microvascular complication with excess mortality when increased levels of urinary albumin loss or reduced filtration function occur. This has an enormous socio-economic impact to the patients, their families and the nation at large.

RATIONALE

Although microalbuminuria reflects an early stage in an irreversible stage of kidney disease in diabetic patients, there are different degrees of progression of microalbuminuria as some studies have demonstrated that microalbuminuria often regresses to normal[8, 52] while other studies show that a significant proportion of patients who initially have microalbuminuria progressing to the irreversible stage of diabetic nephropathy and eventually end stage renal disease. Most of the available information about the patterns of microalbuminuria progression are reports of studies done among Caucasians. No such studies from the available reviews have been done mainly among African patients to describe the progression of microalbuminuria among diabetic patients**.**

BROAD OBJECTIVES

To determine the progression of microalbuminuria in patients with diabetes over a nine year period at MNH

Specific objectives:

a) To determine the proportion of diabetic patients with microalbuminuria who progressed to either macroalbuminuria or ESRF.
b) To determine the factors associated with progression or regression of microalbuminuria among diabetic patients.

CHAPTER TWO

METHODOLOGY

Study design

Retrospective cohort study of type 1 and type 2 diabetic patients with and without microalbuminuria

Study site

The study was conducted at MNH diabetic clinic which is located on southern part of Muhimbili national hospital. This unit provides health services to diabetic patients on outpatient bases by operating twice a week, on Mondays and Thursdays. On Mondays provides diabetic service to diabetic children and on Thursdays to adult diabetic patients.

Study population

The study was conducted basing on available list of participants involved in the baseline study by Lutale et al 2003/2004 at MNH diabetic outpatient clinic.

Description of the baseline study population in 2003/2004.

The baseline study done at MNH by J. Lutale et.al in 2003/2004 comprised of 259 study participants. The baseline study aimed at determining the prevalence of microalbuminuria among African diabetic patients. The study found out that overall prevalence of microalbuminuria was 10.7% and macroalbuminuria 4.9%.[53] The prevalence of microalbuminuria was 12% and 9.8% among type 1 and type 2 respectively. In this study it was apparent that abnormal albumin excretion rate was associated with longer duration of diabetes and significantly higher levels of both systolic and diastolic blood pressure among type 2 diabetes. All patients with or without albuminuria were counselled and treated accordingly, and allowed to continue with medical attention under the care of their attending physician. Because of the importance of blood pressure and glycemic control on the development and progression of microalbuminuria, all patients were instructed to strictly

adhere to medications and have regular test for blood glucose, lipid profile, urine for microalbuminuria and monitor blood pressure regularly. Patients attended as per clinic routines, without a close follow up of the researcher. Therefore this study seeks to determine albuminuria status in this cohort following 9 years elapse period since the baseline study.

At baseline, overnight urine collection was done twice on two consecutive days and the average of the two readings to determine the final urinary excretion rate (AER) was used. AER was then categorized as normoalbuminuria (AER of < 20 µg/min), microalbuminuria (20–200 µg/ min) and macroalbuminuria (> 200 µg/min). Albumin to creatinine ratio (ACR) was calculated and values ≥ 2.5 mg/ mmol for men, ≥ 3.5 mg/mmol for women defined as microalbuminuria. Macroalbuminuria was defined as ACR ≥ 30 mg/mmol for men and women. Details can be obtained from the published data [54]

Patient recruitment

In the follow up study participants were recruited from the original registry of 259 patients involved in the baseline study in 2003/2004. All study participants were actively traced through cross checking all patients attending the routine diabetic clinic in order to identify the study participants existing in the original registry, only patients found to have participated in the baseline study were included in this study. For those study participants who had died before this study their medical information were retrieved through assessment of their clinical files. The major limitation to this active follow up tracing was the fact that majority of study participants were not available due to various reasons including the change of residence, inconsistent attendance (poor medical compliance), some patients attending diabetic clinics at municipal hospitals in the city, also a subset of these patients probably had completely abandoned the medical care to substitute with traditional therapy and lastly some of the patients not seen currently might had died but not known to us**.**

Data collection methods

A standard questionnaire was used to obtain the patient's information regarding diabetes duration and treatment, smoking history, alcohol intake, gender, occupation, education and marital status. The use ACE inhibitors or ARB'S and other antihypertensive were not determined for each participant.

Urine collection

Patients were instructed to collect aseptically clean random spot voided urine into a clean and dry plastic container without preservatives at the diabetic clinic and they were not centrifuged. Testing for urine samples was done within half an hour of collection. Menstruating women were allowed to complete their period before they provided the urine samples.

Measurement of albumin / creatinine ratio (ACR).

All urine samples were screened for infection with a dipstick strip. Patient whose urine samples were found to have hematuria or features of urinary tract infection were initially treated and then instructed to bring urine samples after their recovery.

Urinary albumin was measured initially with a uro-dip 10 [e] dipstick strip. Albuminuria positive by dipstick meant albumin conc. > 300mg/dl (0.3g/L) also termed as macroalbuminuria. Patients with dipstick test positive for albuminuria no further quantitative assays were done. Samples which tested dipstick negative for albuminuria were further tested using a semi-quantitative assay to determine albumin and creatinine concentrations using Urinalysis Reagent Strips a Package Insert (REF:U031-021) . Eventually albumin to creatinine ratio (ACR) was calculated.

Levels of albuminuria were then classified into normalbuminuria, microalbuminuria or macroalbuminuria based on albumin creatinine (ACR) obtained from random urine samples as shown on table below.

Table showing categories of albuminuria according to albumin/creatinine ratio (ACR)

		Albumin/ creatinine ratio	
	Gender	**mg/mmol**	**mg/g**
Normal	M	<2.0	<10
	F	<2.8	<15
Microalbuminuria	M	2.0-20	20-<200
	F	2.8-28	30-<300
Macroalbuminuria	M	>20	>200
	F	>28	>300

Biochemical tests

Blood samples were taken as 5mls of venous blood from the antecubital fossa and placed in empty sterile tubes for estimating serum creatinine, total serum cholesterol, high density lipoproteins, low density lipoprotein and serum triglycerides using Cobas Integra 400 plus (Roche) clinical chemistry analyser.

Assessment of the glycemic control was done at diabetic clinic where by a tip of a finger was pricked by a needle and a drop of blood allowed to fall onto a glucostrip and then measured by using Contour TM TS blood Glucose meter. It was categorized as being normal glycaemic control if fasting blood glucose (FBG) was <6.1mmol/l and or a random blood glucose 7.1-11.0mmol/l and poor glycaemic control if FBG was $\geq$ 6.1mmol/l or a random blood glucose of > 11mmol/l.

Also determination of glycosylated hemoglobin levels was done to assess the level of glycaemic control using Konelab ™ machine@2003 Thermo Electron Corporation. It was categorized as good control when the HbA1c was <7.5% and poor control when HbA1c was ≥ 7.5%.

Renal function tests

Cockcroft Gault formula was used to correlate GFR based on creatinine clearance (Cl_{cr}) which was calculated from the serum creatinine concentration.

In men

$$CL_{cr}\,(ml/min) = \frac{(140-Age) \times wt}{72 \times \text{Serum creatinine (mg/dl)}}$$

In women the calculated values was multiplied by 0.85.

BMI measurement

Weight was measured using an Analogue scale (SECA), with light clothing and recording to the nearest 0.5 kg while the height were measured in centimeter and rounded to the nearest 0.5 cm using a measuring board after the patient had removed his/her shoes and cap. BMI was then obtained from the ratio of weight (in kilograms) to height (in meters) squared. BMI was categorized as underweight when less than 18, normal weight when BMI was between 18–24.9, overweight when was 25–29.9 and BMI of more than 30 categorized as obesity.

Blood pressure measurement.

Arterial blood pressure was measured using manual mercury sphygmomanometer while sitting and recorded to the nearest 5 mmHg. Blood pressure was measured three times separated by 2 minutes and the average measurement was considered to be the patient's blood pressure. The 1st and the 5th Korotokoff's sound were used to determine the systolic (SBP) and diastolic blood pressure (DBP) measurements respectively. Hypertension was defined as SBP ≥140 and/or DBP of ≥90 mmHg or use of hypertensive medication.

Ethical consideration:

Ethical clearance to conduct the study was obtained from Muhimbili University of Health and Allied Science Ethical Review Board while the permission to do this study was obtained from the Hospital management and a written informed consent to participate in the study was sought from the study participants.

Clinical evaluation and laboratory investigation procedures and interpretations were done by qualified registered doctors/ laboratory technicians.

Data entry, cleaning and analysis:

Collected data were checked for completeness and consistency, and errors or discrepancies found were corrected. Data was entered and analyzed using computer software SPSS version 17. Descriptive statistics were obtained for all variables using median and frequency and proportions for categorical variables. Fisher exact test were used to determine the association between the study variables. P-value of <0.05 or less was deemed significant.

CHAPTER THREE

RESULTS

Patient Population

Out of the baseline study population of 259, 183 had normoalbuminuria status, 57 had microalbuminuria and 19 were found to be macroalbuminuric. Out of the 259, 127 study participants could not be traced while 49 study participants were known dead, therefore ending with a total of 83 study participants being recruited in this study. Out of the 83 recruited study participants it was found that 74 had normoalbuminuria at the baseline where as 8 had microalbuminuria and only one was macroalbuminuric at baseline [flow chart 1].

Of the 49 patients who were known to have died, 45.6% of them had microalbuminuria and 47.4% had macroalbuminuria at baseline while only 7.7% had normoalbuminuria.

The mean (±SD) age of 83 participants was 31.9(±13.1) years for type 1 diabetic patients and 56.3(±12.2) years for type 2 diabetic patients and majority (59%) were women. The minimum age was 16 years and the maximum age was 88 years.

At follow up period it was found that among diabetic type 1 participants the mean age, BMI, HbA1C and serum creatinine were significantly higher than estimated at the baseline where as among diabetic type 2 participants the mean age, SBP, BMI and HbA1C were significantly higher at follow up period as compared to baseline. In both diabetic groups DBP and ACR did not change significantly between the baseline and follow up period.

Type 1 diabetic patients were found to be significantly younger population as compared to type 2 diabetic population (Mean age 31.9 yrs versus 56.3 yrs, $P<0.000$), and had poorer glycemic control (mean HbA1c of 10.4% type 1 versus 9.7% type 2 patients, $P= 0.001$). However the mean SBP, DBP, BMI, serum creatinine in type 1 diabetes were lower than in patients with type 2 diabetes [Table 1].

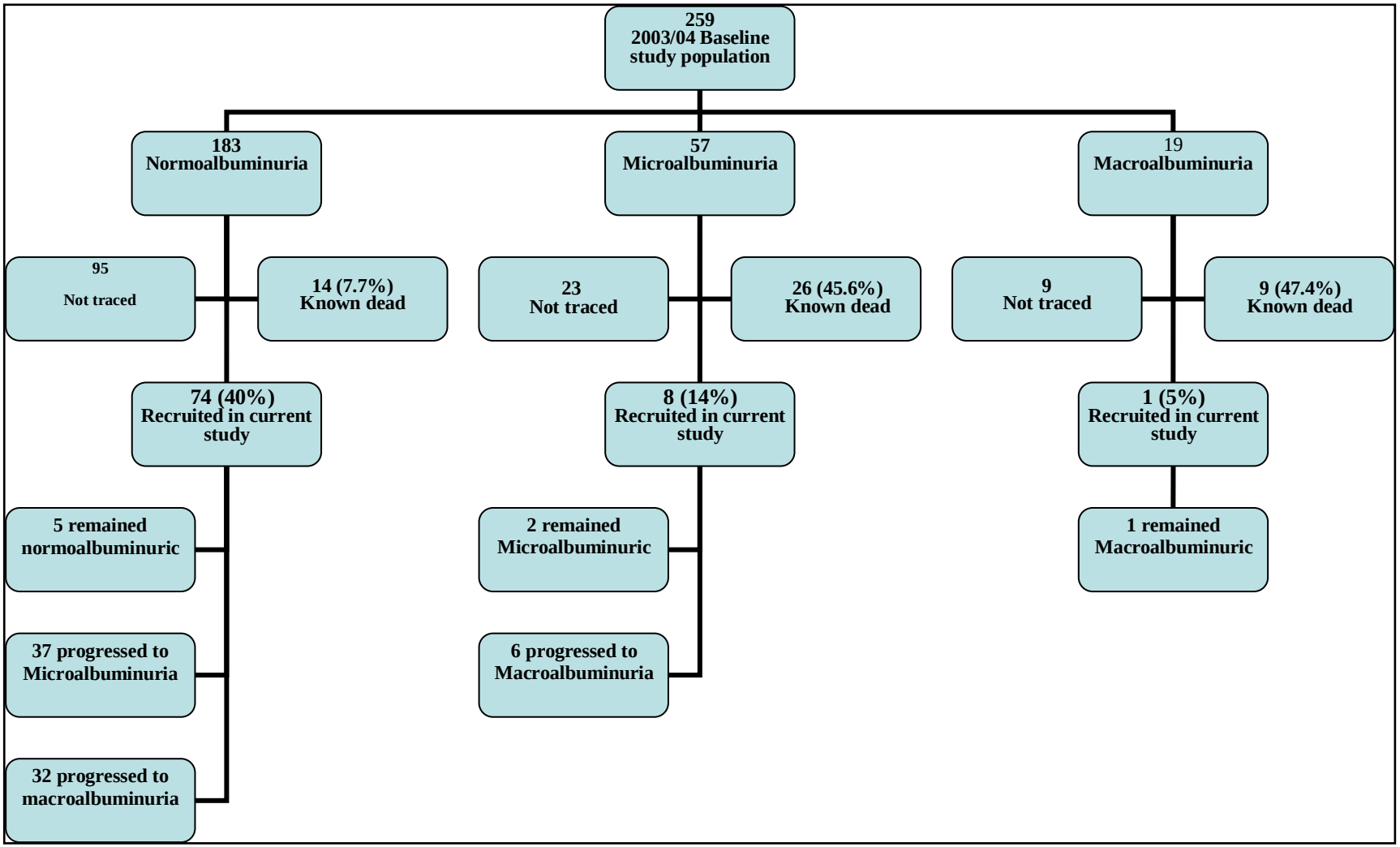


Figure 1.Study flow diagram

Table 1. Summary of albuminuria progression among the 83 recruited patients

Baseline Status	Progression
Normoalbuminuria N=74	5 (6.8%) remained normoalbuminuria
	37 (50%) Progressed to microalbuminuria
	32 (43.2%) Progressed to macroalbuminuria
Microalbuminuria N=8	2 (25%) remained microalbuminuria
	6 (75%) Progressed to macroalbuminuria
Macroalbuminuria N=1	1 (100%) remained macroalbuminuric

Albuminuria progression.

Among the 74 patients with normoalbuminuria at baseline, 5 (6.8%) remained normoalbuminuria, 37 (50%) progressed to microalbuminuria and 32 (43.2%) progressed to overt proteinuria (macroalbuminuria). Whereas among those patients who had microalbuminuria at baseline, 75% progressed to macroalbuminuria and 25% persisted as microalbuminuria while none of them regressed towards normoalbuminuria [Table 1 and flow chart 1].

Table 2: Baseline and follow up Sociodemographic characteristics and basic data of Type 1 and Type 2 diabetic patients. N=83.

	Type 1 (N=35)			**Type 2 (**N=48)		
	Baseline	**Follow-up**	**P-value**	**Baseline**	**Follow-up**	**P-value**
Mean Age (yrs)	24.5±13.6	31.9±13.1	.000	46.5±11.6	56.3±12.2	000
Blood pressure						
SBP	125.3±20	124.7±17.	.890	128.4±24	142.53	.004
DBP	77.6±118	78.4±9.9	.734	84.1±20	84.5±3	.912
BMI(kg/m2)	24.1	25.9	.001	27.2	27.4	.001
HbA1C (%)	12.1	10.4	.001	9.5	9.7	.001
S.creatinine(umol/l)	51.4	93.	.001	74.1	118.8	.792
ACR (mg/g)	13.84	19.4	.097	8.82	15.7	.197

Progression and risk factors associated with microalbuminuria

Majority of patients with microalbuminuria progression occurred in type 1diabetes (83.3%) as compared to among type 2 diabetes patients. It was also shown that as compared to diabetes type 2 patients, diabetic type1 had higher proportion of individuals with microalbuminuria persistence (50%). However despite this notable difference of microalbuminuria progression there was no statistical significance between the two diabetic types as shown on table 3 below.

Diabetic duration

Diabetic duration of 10-15yrs was associated with microalbuminuria progression in majority of patients with diabetes (100%) however diabetic duration of 16-25yrs had majority of diabetic patients with microalbuminuria persistence (40%) as compared to diabetic patient with duration of 10-15yrs.

Level of glycemic control and microalbuminuria progression

Poor glycemic control (HbA1C >10%) was found to be associated with microalbuminuria progression in majority of patients with diabetes (83.3%) while improving glycemic control (HbA1C 8.6-9.9%) was found to be associated with microalbuminuria persistence (50%) as compared to poor glycemic control (HbA1C> 10%) which had more progression than persistence.

Blood pressure control and microalbuminuria progression

Diastolic blood pressure alone and both systolic and diastolic hypertension affected microalbuminuria progression especially so among those with diastolic hypertensive participants, as all (100%) who had microalbuminuria progressed to macroalbuminuria as compared to those with microalbuminuric normotensive diabetics.

Table 3: Various risk factors associated with microalbuminuria progression

Attribute	Progression	Persistence	P-Value
Diabetes			
N=8			
Type1	1 (50%)	1 (50%)	
Type2	5 (83.3%)	1 (16.7%)	.464
Diabetic duration (yrs)			
N=8			
10-15	3 (100.0%)	0(0.0%)	
16-25	3 (60.0%)	2(40.0%)	.464
HbAIC(%)			
N=8			
8.6-9.9	1 (50.0%)	1(50.0%)	
>10	5 (83.3%)	1(16.7%)	.463
Blood pressure			
N=8			
Normotensive	1 (50.0%)	1(50.0%)	
Diastolic hypertension	2 (100%)	0(0.0%)	
Systolic and diastolic hypertension			
	3(75.0%)	1(25.0%)	1.0

All significance according to fisher exact test

The study intended to determine the effect of cigarette smoking on the progression of microalbuminuria as these are among the known risk factors implicated in accelerating microalbuminuria progression, however their effect were not assessed as majority were neither non smoker nor alcohol drinker and few of them were drinking local brews and tobacco sniffing making it difficult to quantify.

CHAPTER FOUR

DISCUSSION

In this study we found that progression of microalbuminuria occurred in many (83%) of patients with diabetes type 2. The risk factors associated with progression were diabetic duration of 10-16yrs, poor glycemic control and high blood pressure either diastolic or systolic and diastolic hypertension.

This was the first research to be conducted in Tanzania that looked at progression of microalbuminuria among diabetic patients; it also looked at risk factors that are implicated in accelerating microalbuminuria progression. The study highlights the importance of screening the risk factors among diabetic patients that may accelerate albuminuria progression.

In this study we also found that among diabetic type 1 patients microalbuminuria progression occurred in 50% of patients. These are discordant findings as compared to previous studies[3,4,5] which showed opposite of these observation, as among type 1 diabetics with persistent microalbuminuria at baseline without intervention approximate 80% progressed to overt nephropathy after a period of 10-15yrs, whereas only 20-40% of diabetic type 2 progressed to overt nephropathy over the same comparable period of time. This discordance could be explained by the fact that our study had few participants and therefore probably these findings were limited to chance variation as we consider it likely that, had they been available, those lost to current study would have changed the outcome of the study.

This high proportion of progressors among patients with diabetes type 2 could be due to observable poor glycemic control on these patients; this observation is in agreement with the suggestion that both chronic exposure to glycaemia and individual susceptibility factors are critical for the pathogenesis of diabetic nephropathy.

In our study this magnitude of progression is again higher than found in previous study done by Bahman et al 2001 in a seven year follow up study which estimated low proportion of

progression of microalbuminuria amounting to 6%. These differences could probably again be explained by presence of large number of study participants who were not available in present study and large loss to follow up (50%) in the 7-yr follow up study by Bahman, that the loss of these patients lead to different observed unrealistic (biased) results in these two studies.

The fact that there was a progressive increase in mortality across the advancing albuminuria category with high proportion of death occurring in participants with macroalbuminuria probably there were albuminuria progression in this population subset leading to renal failure and therefore attributing for their death. On virtue of this information without an exceptional that the untraceable population includes died participants with progressed renal dysfunction, it is likely that the actual proportion of albuminuria progression documented above based on recruited alive participants was underestimated.

This study demonstrated that progression of microalbuminuria was dependent on the duration of diabetes with higher proportional of progressors occurring among microalbuminuric patients with 10 to 15 years of diabetic duration. However this high proportion of progressers with diabetic duration 10-15yrs had non statistical significance difference (P=0.464) as compared to diabetic duration of 16-25yrs.

This finding were in keeping with a ten-year prospective observational study by Peter Rossing et al 2005 conducted in Denmark which aimed to determine the progression of microalbuminuria in type 1 diabetes where it was found that longer duration of microalbuminuria (persistent microalbuminuria) and diabetes had close association with high risk for progression of microalbuminuria to overt proteinuria [30]

In this study we also observed that microalbuminuria progression was highly dependent on glycemic control as high proportion of participants with poor glycemic level (HbA1C>10%) had tendency towards microalbuminuria progression to overt proteinuria. This observation is in accordance with previous observational studies, as it was shown that poor glycemic control was associated with a fast annual rate of progression in albuminuria and high risk of progression to overt nephropathy [15]. In this previous study the incidence rate varied

significantly depending on the level of glycemic control and it was shown that improved glycemic control at HbA1c level of less than 8.5% was associated with reduced progression to overt proteinuria unlike glycemic control above this level.

Our study has also shown that diastolic and both systolic and diastolic pressure remained the risk factors for microalbuminuria progression among patients with diabetes. Similar evidence showed that progression to proteinuria among microalbuminuric patients was influenced by the level of diastolic blood pressure with the dose response relationship being linear for diastolic blood pressure. [15]

In this study it was also shown that microalbuminuria persistence was high among type1 diabetic patients (50%) however no regression to normoalbuminuria was noted in this study compared to the 7-year observation period by Bahman[7] where 56% of the microalbuminuric type 1 diabetic patient became normoalbuminuric while 33% remained microalbuminuric. Of the subjects with type 2 diabetes, four (57%) of the microalbuminuric subjects became normoalbuminuric, three (43%) remained microalbuminuric, and none progressed to diabetic nephropathy.

CHAPTER FIVE

STRENGTH OF THIS STUDY

This is the first study in Tanzania to evaluate the albuminuria progression among diabetic patients hoping that it has laid foundation towards establishment of other big follow up studies based on diabetic patient with persistence microalbuminuria.

RECOMMENDATION

The study had few participants who could be followed up as compared to the baseline participation causing under powering of the present study. This can undermine the generalization of the results. A well designed close followed up study would improve the findings.

CONCLUSION

This study aimed at assessing the progression of microalbuminuria among diabetic patients over nine years at MNH diabetic clinic. The main finding of the study was high rate of microalbuminuria progression which occurred among the diabetic patients. Among the 74 patients with normoalbuminuria at the baseline who could be traced 93.2% of them their albuminuria progressed either to microalbuminuria 37 (50%), or progressed to macroalbuminuria 32 (43.2%). Whereas among those patients who had microalbuminuria at baseline, 75% progressed to macroalbuminuria and 25% persisted as microalbuminuria, none of them regressed towards normoalbuminuria. Additionally we found that progression of albuminuria occurred in both diabetic groups, the majority of progressers (83%) were observed among type 2 diabetic patients. This progression occurred mainly among diabetic patients with diabetic duration 10-15yrs, poor glycemic control (HbA1C >10%) and diastolic or both systolic and diastolic hypertension.

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APPENDICES

Appendix I: Informed Consent Form

ID no…….

Consent to participate in the study on the progression of microalbuminuria in diabetes over a nine – years, a retrospective cohort study at MNH.

Greetings! My name is Yona Gandye, a postgraduate student at MUHAS, investigating on the progression of microalbuminuria in diabetes.

The purpose of the study; To investigate the progression of microalbuminuria in diabetic patients.

What participation involves:

If you agree to participate in the study, you will be interviewed, and a detailed clinical history regarding your health will be requested.

Confidentiality:

All information collected on questionnaires will be entered into computer with special identification number. The questionnaires will be handled with greater secrecy in order to maintain your confidentiality.

Risks: There is no risk associated with this study

Right to withdraw and alternatives: Participating in this study is completely a voluntary choice. Your allowed to withdraw from the study any time and yet continue to receive all services that are normally provided in the hospital.

Benefits: Participating in this study allows you to know your kidney status and options for treatment in case there is kidney disease.

In case of any injury: We do not expect any harm.

Whom to contact: If you have any question about the study or in case of further information, you can contact Yona Gandye 0718722939. If you have questions about your rights as a participant you may contact Prof M Aboud, Chairman of MUHAS Research and Publications Committee.
P.O.BOX 65001 Dar es Salaam. Tel 2150302-6

Signature

Do you agree?

Participant agrees…….. Participant does NOT agree……

I …… have read and understood the content of this form .My questions have been answered and I voluntarily agreed to participate in this study.

Signature of participant…….

Signature of witness…… Date of signed consent…….

Appendix II: Fomu ya Ridhaa (Swahili Version)

Nambari ya usaili …….

Salaaam! Mimi naitwa Yona gandye, ni mwanafunzi wa shahada ya udhamili - Chuo Kikuu cha Sayansi za Afya na Tiba – Muhimbili. Nafanya utafiti kuhusu kuchunguza tatizo/ ugonjwa wa figo kwa wagonjwa wenye kisukari.

Madhumuni ya utafiti

Jinsi ya kushiriki

Kama utakubali kushiriki katika utafiti huu, utaombwa kujibu maswali kadhaa na pia kufanyiwa vipimo vya damu na figo.Vipimo vitafanyika bure bila wewe kuchangia pesa.

Utunzaji wa siri

Taarifa zote zitatunzwa kwa siri kwa kutumia herufi au nambari badala ya jina la mgonjwa.

Madhara /Athari

Hakuna athari au madhara yoyote yanayotegemewa kutokana na ushiriki wako katika utafiti huu.Vipimo hivi ni salama kwa afya ya mama na mtoto na wala hakitoi mionzi inayohatarisha afya

Uhuru wa kushiriki

Una uhuru wa kushiriki au kutoshiriki kwenye utafiti huu, pia unaweza kujitoa wakati wowote. Kama utachagua kutoshiriki au kujitoa kwenye utafiti huu matibabu yako utaendelea kupata kama kawaida.

Faida ya utafiti

Vipimo hivi vya gharama kubwa vitafanywa bure, mgonjwa atafaidika kwa kuhudumiwa na mtafiti pamoja na kupewa rufaa ili ajiunge na clinic ya madaktari bingwa wa magonjwa ya figo.

Ni matumaini yangu kwamba utafiti huu utasaidia kuboresha tiba kwa wagonjwa wengine siku za baadae.Kuna kamati ya kusimamia udhibiti wa utafiti Kamati hii hutoa taarifa za matokeo ya utafiti ambayo huytoa elimu kubwa kuhusu tatizo hili.

Taarifa

Endapo unahitaji kupata maelezo kuhusu haki zako au taarifa zaidi ,wasiliana na Yona Gandye, Mtafiti, kupitia namba ya simu 0718722939 au Prof M M Aboud Mwenyekiti wa Kamati ya Utafiti, MUHAS S.L.P 651001,Dar es salaam, Simu 2150302-6. Je unakubali kushiriki kwenye utafiti? weka alama ya vema(√)

Ndiyo..... **hapana.....**

Mimi ....., nimeelezwa na nimesoma maelezo haya hapo juu na kuyaelewa na Ninakubali kwa hiari yangu kushiriki kwenye utafiti huu

Sahihi ya mgonjwa .....

Sahihi ya ndugu/shahidi .....

Sahihi ya Mtafiti ..... Tarehe……

Appendix III: Questionnaire (English Version)

PROGRESSION OF MICROALBUMINURIA AMONG DIABETIC PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA OVER A NINE YEAR PERIOD.

1. DERMOGRAPHIC CHARACTERISTICS:

Date of interview……Serial number…….

Name…….Date of birth…….

Residency……..Tel……..

Education level.....

Marital status.....

Employed/unemployed……..

History

1. For how long are you diabetes…….year(s)

2. Type of Diabetic?

   1= Type 1 2=Type 2

3. What medications are you using?

   a) Glibenclamide
   b) Chlorpropamide
   c) Metformin
   d) Insulin
   e) Others

4. Family history of diabetes

   1 = Yes 2 = No

5. Are you known hypertensive?

   1=Yes 2= No

6. If yes for how long are you hypertensive?

7. If yes what medications are you on

   a) Beta blocker

   b) ACE –inhibitors

   c) Diuretics

   d) Calcium channel blockers

   e) Others…….

8. Use of other medications……...

9. Family history of hypertension

   1 = Yes 2 = No

10. Have you ever smoked cigarettes?

    1=Yes 2=No 3=Stopped…….yrs (when)

11. If yes, for how long ……..

12. How many cigarettes per day……

13. Do you drink alcohol?

    1. Yes 2=No 3=Stopped……yrs

14. If yes, for how long……

15. How many bottles per day…….

MEASUREMENTS

Anthropometric

16. Weight (kg).....

17. Height (m).....

18. BMI (Kg/m^2).....

19**. Blood pressure (mmHg**)

BP 1st reading…….mmHg

BP 2nd reading (after 5min)…….mmHg

Average BP……..mmHg

Biochemistry

20. Total Cholesterol…….mg/dL

21. HDL……..mg/dL

22. Triglycerides.....mg/dl

23. LDL Cholesterol ....mg/dl

24. Serum creatinine.....mg/dl

24. RBG.....

25.Glycosylated Haemoglobin.....%

26. Urinary Multistix results

Glycosuria

Leucocytosis

Albuminuria

Creatinine

ACR: