LEVEL OF MICROALBUMINURIA AND GLYCATED HAEMOGLOBIN AMONG TYPE 2 *DIABETES MELLITUS* PATIENTS ATTENDING ABUBAKAR TAFAWA BALEWA UNIVERSITY TEACHING HOSPITAL (ATBUTH), BAUCHI, NIGERIA

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DECLARATION

I hereby declare that, this work titled Level of Microalbuminuria and Glycaeted Haemoglobin among Type 2 Diabetes Mellitus Patients Attending Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH), Bauchi, Nigeria" is the product of my own research efforts; undertaken under the supervision of Dr I.U Yarube; and has not been presented, and will not be presented elsewhere for the award of a degree or certificate.

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Rukayya Babale Shu'aibu

(SPS/11/MHP/00010)

CERTIFICATION

This is to certify that the research work of this dissertation titled "Level of Microalbuminuria and Glycaeted Haemoglobin among type 2 diabetes mellitus patients attending Abubakar Tafawa University Teaching Hospital (ATBUTH), Bauchi, Nigeria" and its subsequent preparations by Rukayya Babale Shu'aibu (SPS/11/MHP/00010) were carried out under my supervision.

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APPROVAL

This is to certify that this Dissertation by Rukayya Babale Shu'aibu (SPS/11/MPH/00010) has been examined and approved for the award of the degree of Master of Science (Physiology) by Bayero University, Kano, for its contribution to Knowledge and literary presentation.

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DEDICATION

I dedicate this work to my parents Alh. Babale Shu'aibu and Hajiya Khadija Muhammad.

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LIST OF ABBREVIATIONS USED IN THE DISSERTATION

ACR - Albumin Creatinine Ratio

ACE- Angiotensin Converting Enzyme Inhibitor

ADA - American Diabetes Association

AER - Albumin Excretion Rates

AIDS - Acquired Immuno Deficiency Syndrome

ARBS - Angiotensin Receptor Blockers

ARIC - Atherosclerosis risk in adjusted communities

ATBUTH - Abubakar Tafawa Balewa University Teaching hospital

BMI - Body mass index

CCF- Congestive Cardiac Failure

CIT - Conventional Insulin Treatment

DALYs - Disability-adjusted life-years

DCCT - Diabetes Control and Complication Trial

D M - Diabetes Mellitus

EDIP - *Early Diabetes Intervention Program*

ESRD - *End Stage Renal Disease*

FPG - Fasting plasma glucose

GDM - Gestational diabetes mellitus

GFR - Glomerular filtration rate

HbA1c - Glycaeted Haemoglobin

HOPE- Heart Outcomes Prevention Evaluation.

HR- Hazard Ratio

HIV - Human Immuno Deficiency Syndrome

HLA - Human leucocyte antigen

ICD- International Classification of Diseases

IDF - International Diabetes Federation

IDDM - Insulin Dependent Diabetes Mellitus

IFG - Impaired fasting glucose

IDNT - Irbesartan Diabetic Nephrology Trial

IGT - Impaired glucose tolerance

IRMA - Irbesartan In Type 2 Diabetes Mellitus and Microabuminuria

MIT- Multiple Insulin Treatment

MARVAL - Microalbuminuria Reduction with Valsatan Trial

N C D - Non Communicable Disease

NGSP - National Glycohemoglobin Standardisation Programme

NIDDM- Non-insulin Dependent Diabetes Mellitus

OGTT - Oral glucose tolerance test

RAAS - Renin Angiotensin Aldosterone System

S D - Standard Deviation

T1DM - Type 1 Diabètes Mellitus

T2DM - Type 2 Diabètes Mellitus

UAE - Urinary Albumin Excretion

UKPDS - United Kingdom Prospective Diabetes Study

US- United States

UTI- Urinary Tract Infection

USD- United States Dollars

WHO - World Health Organization

WHR - Waist to Hip Ratio

$- United States Dollar Currency

ABSTRACT

Type 2 diabetes mellitus is associated with microvascular complications, which can be detected early using specific biomarkers such as micro-albuminuria to detect early stage of renal impairment, and glycaeted hemoglobin for determination of glycaemic controls. The aim of the study was to determine the level of micro-albuminuria and glycaeted haemoglobin in patients with type 2 diabetes mellitus, and its relationship with some selected diabetic complications. Six hundred and fourty three patients were recruited in the study. About three hundred and fourteen cases were selected from the diabetic clinic using systematic sampling, and three hundred and twenty nine control subjects were selected from hypertensive clinic. The levels of Microalbuminuria were tested using Micral test strip, and glycaeted haemoglobin using Quo Laboratory glycaeted haemoglobin machine. Overall prevalence of microalbuminuria among diabetic patients was 30.9% and that of control was 17.6%; while abnormal levels of glycaeted haemoglobin (> 6.5%) among diabetic was 68.5%, and that of control was 4.9%. There was no association between micro-albuminuria and decreased urine volume and visual disturbance. There was an association between micro – albuminuria and retinopathy. There was no association between glycaeted haemoglobin and decreased urine volume, visual disturbance and retinopathy. It was concluded that the prevalence of microalbuminuria is high among diabetics compared to non-diabetic controls. Levels of serum glycaeted haemoglobin were abnormally high among diabetics, when compared to non-diabetic controls. Retinopathy, visual disturbance and decreased urine volume were found to be prevalent among diabetics compared to non diabetic controls. Microalbuminuria was associated with retinopathy, but not with visual problems and decreased urine volume, while high glycaeted haemoglobin levels were not associated with any of retinopathy, visual problem and decreased urine volume. It was recommended that all diabetic patients should be screened early and routinely for microalbuminuria and glycaeted haemoglobin for early intervention to prevent microvascular complication.

CHAPTER ONE

INTRODUCTION

1.0 INTRODUCTION

Diabetes is a group of metabolic deseases characterized by hyperglycemia resulting from defects in insulin secretion, action or both (ADA, 2010). The world prevalence of DM in 2010 was 6.6% with estimated number of 285 million people, and by 2030 the number may reach 552 million (IDF, 2010). Diabetes is usually irreversible although patient can live a reasonably normal life. Its late complications result in reduced life expectancy due to macro-vascular and micro-vascular complications such as coronary artery disease, peripheral vascular disease, stroke, diabetic retinopathy, nephropathy and neuropathy (ADA, 2010).

There are two major types of diabetes mellitus (DM) - type 1 and type 2. Type 1 DM has immune pathogenesis characterized by insulin deficiency, and usually affects the young. Type 2 DM, which results from a combination of insulin resistance and less severe insulin deficiency, is a common condition in population enjoying affluent lifestyle (Kumar and Clark, 2012).

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in several countries (Lopes, 2009). In a study Bittar *et al*. (2012) discovered diabetes mellitus as a cause of chronic hemodialysis and renal transplantation. Several studies have suggested that detection of early changes in renal function via microalbuminuria tests prevents further progression of the disease (Cordonnier *et al*., 1993; Niskance and Laasko, 1993; Varghese *et al*., 2001; Ahmedini *et al*., 2005). Microalbuminuria is common, with

prevalence rates of 10-48%, and is a well-established risk factor for macro-vascular diseases in type 2 diabetes (Kumar and Clark, 2012).

Microalbuminuria is defined as urinary albumin excretion rate of 20-200 μg/min or urinary protein excretion rate of 30-300 mg/day. It predicts future development of overt nephropathy (Ochodnicky *et al*., 2006). Bruno *et al.* (2003) showed microalbuminuria can be reversed, and hence, the future development of overt diabetic nephropathy can be significantly reduced. Screening for microalbuminuria and timely therapeutic intervention has become standard of care worldwide (Bruno, *et al.,* 2003). Microalbuminuria is also considered to be a predictor for cardiovascular disease both among diabetic and non-diabetic subjects (Damsgaard *et al.,* 1990; Yuyun, 2003) and is one of the components of the metabolic syndrome (insulin resistance syndrome). Groop, *et al.* (1993) and Niskance and Laasko (1993) suggested that micro-albuminuria (MAU) represents the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease. Discovered MAU represents an independent predictor or rather a marker of organ damage, since mechanisms linking MAU with end-organ damage have not been fully explained (Ochodnicky *et al*., 2006).

The presence of micro-albumin in the urine of persons with type 2 diabetes is perhaps the most important early signal heralding the onset of systemic vasculopathy and associated with target organ damage (the brain, the heart, and the kidneys), (Kumar and Clark, 2012). Micro-albuminuria also identifies patients who need more rigorous cardiovascular risk management, especially more intensive blood pressure control, and strict attention to glycemic control and lipid levels (Weir, 2004).

One of the central functions of the kidney is the excretion of low molecular weight, water-soluble, plasma waste products into the urine, whereas macro-molecules the size of albumin and larger, are retained (Weir, 2004). The flow of the glomerular filtrate is thought to follow an extracellular route, passing through the endothelial fenestrae, then across the glomerular basement membrane, and finally through the slit diaphragm between the foot processes of podocytes (Weir, 2004). It has been recently hypothesized that micro-albuminuria leading to proteinuria and end-stage renal disease is mainly due to an altered glomerular filtration barrier at the podocyte level (Weir, 2004). However, arterial hypertension and abnormalities of blood lipid concentrations and structure are also important antecedents of such complications in diabetes mellitus. Interestingly, it has been suggested that hyperglycemia, arterial hypertension, and dyslipidemia cause disorders of the albumin excretion rate by damaging the podocyte and slit diaphragm protein scaffold with overproduction of and extracellular release of oxygen radical species at the glomerular level (Nosadini and Tonolo, 2003).

Glycosylated hemoglobin (HbA_{1c}) is a blood glucose control marker in diabetic patients. HbA_{1c} results from post-translation changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks (Nosadini and Tonolo, 2003). Glycosylation of hemoglobin takes place under physiological conditions by a reaction between glucose and N-terminal valine of beta-chain of molecules (Kareem *et al*., 2004). Higher levels of HbA_{1C} were associated with increased risk for development of micro-angiopathy in diabetes. This may be due to the fact that HbA_{1c} has special affinity for oxygen thereby causing tissue anoxia and plays a role in causation of micro- and macro-angiopathy. Davis *et al*. (1978) have shown a positive correlation between

micro-albuminuria and HbA_{1c}. Their findings had since become an important and an interesting aspect for detailed study (Schimitz and Vacth, 1987; Nelson *et al*., 1989; Gupta *et al*., 1991; John *et al*., 1991).

The oral glucose tolerance test (OGTT) is regarded as the "gold standard" for the diagnosis of diabetes mellitus (DM) and impaired glucose regulation (IGR). However, the OGTT is poorly reproducible, time-consuming, and unsuitable for large-scale screening (Bennett *et al*., 2007). Clinicians have begun to recognize that point-of-care blood glucose testing cannot accurately monitor glycaemic fluctuation, or "drift of glucose" and its clinical significance (ADA, 2011). Glycaeted hemoglobin (HbA_{1c}) is an indicator that reflects the average plasma glucose levels over the recent 2 to 3 months. The HbA_{1c} test is relatively stable and has less variability and fewer interference with environmental factors than point-of-care glucose testing (Bennett *et al*., 2007; Weykamp, John and Mosca, 2009).

Clinical testing to assess levels of disease control and progression among persons with type 1 and type 2 diabetes mellitus is widely recommended to clinicians to improve patients' clinical outcomes. Two important foci of recommendations for the follow up care of individuals with diabetes include monitoring of glycaemic status by measurement of glycaeted hemoglobin and screening for kidney disease with urine albumin to assess overall disease progression and to detect potential progression toward end-organ damage (ADA, 2010). According to the American Diabetes Association's (ADA, 2010) Clinical Practice recommendations, monitoring of glycemic status is considered a cornerstone of diabetes care and affects how physicians and patients adjust medical therapy as well as behavioral therapy (e.g. diet and exercise). Screening for urine albumin among persons

with diabetes is also widely recommended for the detection and treatment of incipient diabetic nephropathy and affects the physician's implementation of therapy to slow progression of kidney disease (ADA, 2010).

Recently, the application of HbA1c in the diagnosis of DM was fully endorsed by The ADA in an updated and promulgated 2010 version of "The Clinical Practice Recommendations for the Diagnosis and Treatment of Diabetes (ADA, 2010).

1.1 STATEMENT OF RESEARCH PROBLEM

Diabetes has become worldwide burden, with prevalence estimated at 285million people in 2010. Based on current trends, International Diabetes Federation (IDF) projects that 592 million individuals will have diabetes by the year 2035 (IDF, 2014). In Nigeria study done in North Eastern region prevalence of diabetes was 7% (Gezawa *et al.,* 2015), Prevalence of type 2 diabetes mellitus is rising much more rapidly because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of population (Kumar and Clark, 2012). Type 2 diabetes mellitus is associated with several microvascular complications such as diabetic nephropathy and retinopathy (ADA, 2010).

1.2 JUSTIFICATION FOR THE STUDY

The data to be obtained in this study may reveal the nature and magnitude of micro-albuminuria and serum glycaeted haemoglobin among diabetes patients in the study area. The study may also provide evidence to justify the use of micro-albuminuria as early sign of diabetes complications, and glycaeted haemoglobin as marker of long-term glycaemic control among patients in the study area. There are various markers that can be used for early detection of these complications (ADA, 2010). These include micro-albuminuria to

detect early stage of renal impairment, glycaeted hemoglobin for determination of glycaemic control, duration and risk of developing diabetic complications (ADA, 2010). One of such studies conducted by Litwak *et al.* (2013) revealed that complication rates where high 27% had macrovascular complications and 37% had microvascular complications. Though many studies have been conducted to assess micro-albuminuria and level of glycaeted haemoglobin among diabetic patients (Andrzey *et al.,* 1995; Weycamp, 2009; ADA, 2010; Sureh and Ivvala, 2013) few of such studies have been done in our environment.

1.3 SIGNIFICANCE OF THE STUDY

The results of the study enable us to find out magnitude of diabetic complication such as microalbuminuria and retinopathy among patient resident in the area. The result will provide justification for use of glycaeted haemolobin for long term monitoring of diabetic patient in our enviroment and relationship between some complications, example micro-albuminuria and retinophathy, shows that one is depended on presence of the other.

1.4 AIM OF THE STUDY

The aim of the study is to determine the level of micro-albuminuria and glycaeted haemoglobin in patients with type 2 diabetes mellitus, and its relationship with some selected diabetic complications.

1.5 SPECIFIC OBJECTIVES OF THE STUDY

1) To determine micro -albuminuria in urine samples of the patients (Diabetic and controls) selected for the study.

2) To determine the level of fasting blood sugar and glycaeted haemoglobin of the patients (Diabetic and controls)

3) To clinically assess the subjects (Diabetic and controls) for presence or absence of some selected diabetic complications like retinopathy and microalbuminuria.

4) To examine the relationship between micro-albuminuria and glycaeted haemoglobin, with presence or absence of diabetic complications like retinopathy.

1.6 STATEMENT OF RESEARCH HYPOTHESES

The null hypotheses (Ho):

1) There is no difference in the level of micro-albuminuria, glycaeted haemoglobin and fasting blood sugar between type 2 DM patients compared to control.
2) There is no difference in Signs and symptoms of diabetic complications between type 2 DM patients and to control.
3) There is no relationship between the level of micro-albuminuria and glycaeted haemoglobin and signs and symptoms of diabetic complications.

CHAPTER TWO

LITERATURE REVIEW

2.0 INTRODUCTION

Diabetes mellitus (DM) is a complex, chronic disease. It is a condition characterised by an elevation of the level of glucose in the blood (ADA, 2010). Insulin, a hormone produced by the pancreas, controls the blood glucose level by regulating the production and storage of glucose. In diabetes there may be a decrease in the body's ability to respond to insulin or a decrease in the insulin produced by the pancrease which leads to abnormalities in the metabolism of carbohydrates, proteins and fats (Kumar and Clark, 2012). The resulting hyperglycaemia may lead to acute metabolic complications including ketoacidosis and in the long term contribute to chronic micro-vascular complications (Stephen *et al*., 2013). Mohsin *et al.* (2015) defined diabetes mellitus as a complex, chronic disorder characterised by disruption of normal carbohydrates, fat and protein metabolism and the development of complications over time. Its late complications result in reduced life expectancy due to macro-vascular and micro-vascular complications such as coronary artery disease, peripheral vascular disease, stroke, diabetic retinopathy, nephropathy and neuropathy (Kumar and Clark, 2012).

Vasantha *et al.* (2015) defined diabetes mellitus as a metabolic disorder characterized by glucose intolerance. It is a systemic disease caused by an imbalance between insulin supply and insulin demand. The onset is from 3 years in children and 25 years in adults. According to WHO (2011), the criteria for diagnosis of diabetes mellitus have been explained as plasma glucose of 11.1mmo1/L or higher, or fasting plasma glucose of 7.0mmo1/L or higher. According to Hassan *et al.* (2015), the prevalence of

diabetes is higher in minority groups and among those who are socio-economically disadvantaged, but the reason for that has not been given.

2.1 EPIDEMIOLOGY OF DIABETES MELLITUS

The world prevalence of DM in 2010 was 6.6% (Kumar and Clark, 2012). The world prevalence of DM in 2014 increased to 8.3% (IDF, 2014).

The prevalence of type 2 diabetes has increased in recent decades to epidemic proportions (King, *et al*., 1998). About 150 million individuals worldwide had type 2 diabetes in 2000, and this number is expected to increase to 300 million by the year 2025 (King, *et al*., 1998). In Africa, the estimated prevalence of diabetes is 1% in rural areas, up to 7% in urban sub-Sahara Africa, and between 8-13% in more developed areas such as South Africa and in population of Indian origin (motala, 2012). Seventeen studies performed in 10 countries since 1984, using WHO criteria, have shown rates ranging from 0% in Togo to 4.8-8% in South Africa, and up to 10% in Northern Sudan (King, *et al*., 1998). Nigeria's DM prevalence based on the 1997 National Expert Committee report on Non-communicable Disease (NCD) was 2.2% with a male: female ratio of 1.1:1 (Pueppet, 1996; Akinkugbe *et al*., 1997).

The prevalence of diabetes mellitus (DM) has more than doubled in the last two decades in Nigeria (Oputa and Chinenye, 2012). Ohwovoriole recorded 1.7% in lagos metropoly (Ohwovoriole *et al*., 1988). In Jos, North Central Nigeria the prevalence was 3.2% as at 1996 (Pueppet, 1996). Oyegbade *et al.* (2007) put the prevalence at Ife to be 4.62% and Dahiru *et al*. (2008) in semi- urban Zaria, Northern Nigeria in 2008 reported 2.0%. NCD (1997) found the prevalence in urban Kano to be 1.8%, another study done in North

Eastern Nigeria showed crude DM prevalence of 7% (Gezawa *et al*., 2015). This is further highlighted by the study of Nyenwe *et al.* (2003), which showed a crude DM prevalence of 6.8% in the oil rich Port Harcourt, Nigeria in 2003. Other factors of less importance are physical activity, family history, smoking and alcohol consumption (Nyenwe *et al*., 2003).

2.2 BURDEN OF DIABETES MELLITUS

Diabetes Mellitus is a disease with significant impact on the health of affected individuals, their quality of life and life expectancy, as well as on the health-care system as a whole (Kolawole and Olugbode, 2012). Diabetic patients have a higher hospitalization rate, longer hospital stay, and increased ambulatory care visits (Wild *et al*., 2000; Kolawole and Olugbode, 2012).

The increased morbidity and mortality among diabetics are associated with heavy economic losses. Diabetes is a significant cause of adult blindness in the non-elderly, and a leading cause of non-traumatic amputation in adults, as well as the third cause of nephropathy requiring dialysis in our environment (King *et al*., 1998; Bamgboye, 2006).

Patients with DM are prone to severe form of infections like perinephric abscesses, emphysematous cystitis, pyelonephritis, renal papillary necrosis and gram negative septicaemia (King *et al*., 1998; Bamgboye, 2006). Diabetics are also prone to certain infections such as pseudomonas “malignant” otitis externa, monilial skin infections, and rhino cerebral mucormycosis. Cognitive impairment has also been identified in diabetic patients (Bamgboye, 2006). Diabetes was estimated to cause 3.8 million deaths worldwide in 2007, about 6% of total global mortality, about the same as HIV/AIDS

(Medalen and Finkel, 2011). Using World Health Organization (WHO) figures on years of life lost per person dying of diabetes, this translates into more than 25 million years of life lost each year (King *et al*., 1998). A study conducted by the World Bank found that of the 1,362 million disability-adjusted life-years (DALYs) lost to all illnesses in 1990; 7.97 million DALYs were lost because of diabetes (Jonsson, 2012). The International Diabetes Federation (IDF) estimates that the equivalent of an additional 23 million years of life are lost to the disability and to reduced quality of life caused by the preventable complications of diabetes (King *et al*., 1998). It is often the case that caring for diabetes steals valuable time from education, paid work and leisure. In many countries, individuals and families fear and experience the disability, reduced quality of life, and the lost years of life that untreated diabetes brings (King *et al*., 1998).

2.2.1 Economic Burden of Diabetes Mellitus

People living with diabetes and their families feel the impact of diabetes most directly. They feel the often crushing expenses of diabetes treatments as costs are not subsidized, and family income is frequently reduced when diabetes interferes with work (King *et al*., 1998).

Because of the chronic course of type 2 diabetes and the significant morbidity and mortality associated with the vascular complications of the disease, type 2 diabetes has become not only a serious public health threat, but also a heavy economic burden on the health care system (ADA, 2007).

The total annual cost of diabetes care in the U.S. in 2007 is $174 billion, including $116 billion in excess medical expenditures and $58 billion in reduced national productivity.

Medical costs attributed to diabetes include $27 billion for care to directly treat diabetes, $58 billion to treat the portion of diabetes-related chronic complications that are attributed to diabetes, and $31 billon in excess general medical costs (ADA, 2007). The largest components of medical expenditures attributed to diabetes are hospital inpatient care (50% of total cost), diabetes medication and supplies (12%), retail prescriptions to treat complications of diabetes (11%), and physician office visits (9%). People with diagnosed diabetes incur average expenditures of $11,744 per year, of which $6,649 is attributed to diabetes (ADA, 2007). People with diagnosed diabetes, on average, have medical expenditures that are 2.3 times higher than what expenditures would be in the absence of diabetes (King *et al*., 1998; Ralph *et al*., 2013). In the UAE, in Al ain Hospital, it was estimated that the total annual direct treatment costs of DM among patients without complications, was US $1,605 (SD = 1,206) which is 3.2 times higher than the per capita expenditure for health care in the UAE (US$ 497) during 2004 (WHO, 2011). However, this cost increased 2.2 times with the presence of DM related complications for patients with microvascular complications, by 6.4 times for patients with macrovascular complications and 9.4 times for patients with both micro and macrovascular complications (AL-Maskari *et al*., 2010).

There are however no sufficient data on the economic burden of diabetes in Nigeria, However, Oyegbade *et al.* (2007) in Ife studied a cohort of 94 patients, 83% of whom were in the low socioeconomic class, with an average clinic attendance of 8 months and average duration of hospital stay as 38 days. The total cost of insulin, oral hypoglycaemics, other drugs and laboratory test was $51,986.00 (oyegbade *et al.*, 2007), while another study at the University College Hospital, Ibadan puts the mean and median

daily cost of medications to the patients at N183.5 ±150.4 and N 156 (Nigerian Naira), approx $1.42 and $1.2 (USD) respectively (Enwere *et al*., 2006).

The epidemiological studies by Zimmet *et al.* (1994) and the World Health Organization included estimates of increased prevalence of diabetes resulting from an increase in population. Estimates of the global cost of diabetes based on these studies reveal that diabetes accounts for 2-3% of the total health care budget in every country; therefore, an increase in diabetes incidence and prevalence translates into a significant economic impact (Jonsson, 2012).

These results suggest that primary prevention of type 2 diabetes could be an effective strategy to restrain the epidemic increase in the disease prevalence and reduce the economic burden it poses on the health care system. In the long run, prevention strategies will only be effective with prompt and early diagnosis before the patients develop the complications most of which are preventable.

2.3 CLASSIFICATION OF DIABETES

There are four major classifications of diabetes mellitus, namely: Type I, Type II, Others

Type III and Gestational Diabetes mellitus (WHO, 2011).

2.3.1 Type I Diabetes Mellitus

This is known as insulin depended diabetes mellitus (IDDM) about 5-10% of patients have type I diabetes mellitus. The pancreas produces inadequate amounts of insulin, resulting in the need for insulin injections to control the blood glucose. It is characterised by a sudden onset, usually before the age of 30 years (Mohsin et al., 2015). According to

Kumar and Clark (2012), in type I diabetes, auto-immune B-cell destruction is attributed to a genetic predisposition coupled with viral agents and possibly chemical agents. Individuals susceptible to type I diabetes are linked to HLA (Human Leucocytes Antigen) DR3 and DR4 loci (DR3 and DR4 are just numbers used to identify the antigens).

2.3.2 Type II Diabetes Mellitus

This is also known as the non insulin dependent diabetes mellitus NIDDM. It results from a decrease in the sensitivity of the cells to insulin and a decrease in the amount of insulin produced. About 90-95% of patients have type II diabetes. This type II diabetes is treated with diet and exercise, and if elevated glucose levels persist, diet is supplemented with oral hypoglycaemic agents. During periods of illness or surgery, individuals who usually control their type II diabetes with diet, exercise and oral agents, may require insulin injections. In some individuals oral agents fail to control hyperglycaemia and insulin injection is required (Mohsin *et al.,* 2015). Kumar and Clark, (2012) indicate that type II diabetes accounts for 80-90% of all cases and is the significant cause of morbidity in the United States. The complications of type II result in disruption of lifestyle, psychosocial adjustment and health care expenses. It is often treated with diet, exercise, self-monitoring of blood glucose and hypoglycaemic agents/insulin, there are two subtypes of type II, obese and non obese. Type II has a strong genetic influence but there is no correlation with HLA (Human Leucocytes Antigen) type. Individuals with type II diabetes have a 50% chance of transmitting the disease to their children

2.3.3 Other Types of Diabetes Mellitus

This is where diabetes mellitus is associated with other conditions, for example, pancreatic disease, hormonal disorders and drugs such as glucocorticoids and oestrogen-containing preparations. Depending on the ability of the pancreas to produce insulin, the patient may require oral agents or insulin (Stephen *et al*., 2013).

2.3.4 Gestational Diabetes Mellitus

The onset of Gestational diabetes mellitus is during pregnancy, usually in the second or third trimester, as a result of hormones secreted by the placenta, which inhibit the action of insulin. It occurs in about 2-5% of all pregnancies. About 30-40% of patients with Gestational diabetes mellitus will develop type II diabetes within 5-10 years (especially if obese). Impaired glucose tolerance and statistical risk groups are examples of Gestational diabetes mellitus. Statistical risk groups are individuals at greater risk than the general population of developing diabetes, and the risk factors include immediate family members with the disease and presence of islet cell antibodies (Stephen *et al*., 2013; Mohsin *et al*., 2015).

2.4 DIAGNOSIS OF DIABETES MELLITUS

Diabetes was originally identified by the presence of glucose in the urine (ADA, 2007). Almost 2,500 years ago it was noticed that ants were attracted to the urine of some individuals. In the 18th and 19th centuries, the sweet taste of urine was used for diagnosis before chemical methods became available to detect sugars in the urine (ADA, 2007). Tests to measure glucose in the blood were developed over 100 years ago, and

hyperglycemia subsequently became the sole criterion recommended for the diagnosis of diabetes. The diagnosis of diabetes mellitus (WHO, 2011).

2.4.1 World Health Organisation Criteria For Diagnosing Diabetes Mellitus

Defined normal fasting plasma glucose (FPG) as <110mg/dl (<6.1mmol/l) as upper limit of normal, impaired fasting plasma glucose ranges from 6.1mmol/l (110mg/dl) to 6.9mmol/l (125mg/dl). First criterion for diagnosing Diabetes is based on presence of Diabetes symptoms (ie polyuria, polydipsia and unexplained weight loss) plus a random venous plasma glucose concentration $\geq$ 11.1 mmol/l **or** a fasting plasma glucose concentration $\geq$ 7.0 mmol/l (whole blood $\geq$ 6.1mmol/l) **or** two hour plasma glucose concentration $\geq$ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT). With no symptoms diagnosis should not be based on a single glucose determination but requires confirmatory plasma venous determination. At least one additional glucose test result on another day with a value in the diabetic range is essential, either fasting, from a random sample or from the two hour post glucose load. If the fasting or random values are not diagnostic the two hour value should be used (WHO, 2011).

2.4.2 American Diabetes Association 2010 Criteria for the Diagnosis of Diabetes Mellitus

The following criteria are considered for the diagnosis of DM:

1. HbA_{1C} >6.5%. The test should be performed in a laboratory using a method of National Glycohemoglobin standardization programme (NGSP) certified and standardized to the Diabetes control and complication trial (DCCT) assay.

2. FPG >126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

3. 2-h plasma glucose >200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dl (11.1 mmol/l). In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing (ADA, 2010).

2.5 GLYCAETED HAEMOGLOBIN

HbA_{1C} testing was first proposed as a measure of blood glucose control in 1976 and has developed into the standardized measure that is now broadly used for both research and clinical purposes (Mary *and Cox,* 2002). Its major practical advantages are that it can be obtained in both fasting and non-fasting states, compared to fasting blood glucose and OGTT that both require fasting. Secondly it represents average glucose control over a period of months rather than a single point value seen in glucose assay for FPG and OGTT (ADA, 2011). Even though HbA_{1C} has been widely accepted since the mid-1990s as the gold standard for therapy assessment and prognostication, it was only in June 2009 that the test was endorsed by the ADA as a first-line test for screening and diagnosis (ADA, 2011). HbA_{1c} assay is convenient for the patient with ease of sample collection for testing (which can be obtained at any time, requires no patient preparation, and is relatively stable at room temperature) compared with that of FPG testing (which requires a timed sample after at least an 8-h fast and which is unstable at room temperature) has led to a lot of debate on the general suitability of the use of HbA1c for the diagnosis of

diabetes mellitus. Therefore HbA_{1c} provides a better index of overall glycemic exposure and risk for long-term complications, with less biologic variability, less pre-analytic instability with no need for fasting or timed samples, less affected by acute (e.g., stress or illness related) or perturbations in glucose levels (ADA, 2011).

At approximately the same time, the International Expert Committee released the formal recommendation of an HbA_{1c} level $\geq 6.5\%$ for diabetes diagnosis. Numerous studies have been done to determine the sensitivity and specificity of A_{1C} testing using definitions based on FPG, 2-hour plasma glucose, and prevalence and incidence of complications (ADA, 2011). In diabetic patients. The term "glycaeted haemoglobin" is a generic one which includes haemoglobin A_1 (HbA_1), HbA_{1c} and total glycaeted haemoglobin. In recent years, improved analytical techniques have resulted in HbA_{1c} supplanting HbA_1 to become the predominant measure of glycaeted haemoglobin (Eric, 2000).

Glycaeted haemoglobin is formed by a post-translational, non-enzymatic, substrate-dependent irreversible process of combination of aldehyde group of glucose and other hexoses with the terminal valine of the ß chain of haemoglobin (Rajini, 2011).

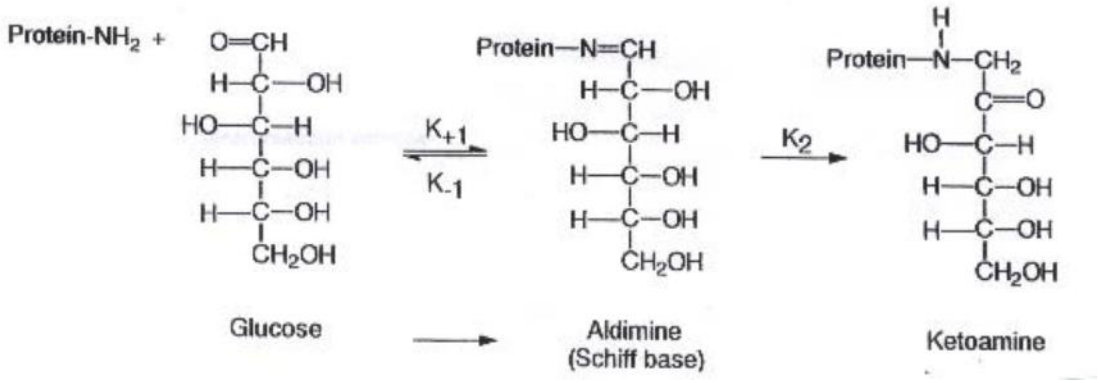

Fig. 2.1.Glycation of Haemoglobin (Adapted from W.H.O Laboratory Diagnosis and Monitoring Of Diabetes Mellitus 2002).

In the last two decades, hemoglobin A_{1C} (A_{1C}) assay has become the gold-standard measurement of chronic hyperglycemia (ADA, 2007). This has been anchored in the knowledge that elevated A_{1C} values increase the likelihood of the microvascular complications of diabetes and perhaps macrovascular complications as well as depicted by (Devid et al, 2014; UKPDS, 1998). Since then, clinicians have used A_{1C} test results to guide treatment decisions, and the assay has become the cornerstone for the assessment of diabetes care (UKPDS, 1998).

2.5.1 Glycaeted Haemoglobin for Diagnosis of Diabetes Mellitus

The hall mark of diabetes is the chronic sustained hyperglycaemia which results ultimately in the manifestation of complications. Studies have consistently shown that there is a strong relationship between the development of retinopathy in diabetic patients and HbA_{1C}, and however, less consistent relationship with fasting plasma glucose levels (Eric, 2000).

Since the ultimate goal and basis of diabetes management is the prevention of diabetes related complications, and the objective can be best achieved when the disease is detected at an early stage. In view of the above, ADA expert committee introduced a new category defined as individuals with FPG levels between 6.1 – 6.9mmol/l called the impaired fasting glucose in order to alert physicians to pursuing patients at risk (Clark *et al*., 2001).

Sequel to the recommendations of ADA (2010) which stipulates the use of HbA_{1c} for the diagnosis of diabetes, WHO (2011) also came up with a recommendation that HbA_{1c} can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are

in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA_{1c} of 6.5% was therefore recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests (WHO, 2011). Despite that, large volume of data from diverse population studies has now shown that HbA_{1C} is associated with increased prevalence of moderate retinopathy and provides a strong justification for assessing an HbA_{1C} of >6.5% cut off point for diagnosis of diabetes mellitus (Rajin and Bhawesh, 2011).

Clark *et al.* (2001) in the EDIP study found the ability of an elevated HbA_{1C} level than plasma glucose to detect diabetes in their cohort of 101 high risk patients to be significantly higher (61% CI 51-71 vs 45% CI 35-55), respectively, P = 0.002) . Only 45% of OGTT diagnosed diabetes exhibited initial FPG levels > 7.0mmol/l. They also noted that 56% of the subjects with FPG levels between 5.0-6.9mmol/l 24(43%) exhibited an elevated HbA_{1C}. Thus, they concluded that individuals with FPG levels between 5.5 and 8.0mmol/l have a 50% chance of actually having diabetes as diagnosed by OGTT criteria; hence HbA_{1C} should be used for the routine diagnosis of diabetes.

2.5.2 Glycaeted Haemoglobin and Estimated Average Glucose

The clinical world has assumed that the A_{1C} assay reflects average glycemia over the preceding few months. However, the data supporting that premise are not exceptionally robust (Eric, 2000; ADA, 2007). Although some clinicians are already providing patients with their "average blood glucose," by simply converting the current A_{1C} test results to a term more relevant to the values obtained from patient self-monitoring, a more accurate

conversion algorithm has been extrapolated on the work of the National Glycohemoglobin Standardization Program (NGSP) in the U.S. and other similar programs in other parts of the world, the current A_{1C} assay has been harmonized on reference methods that measure a mixture of glycaeted hemoglobins (ADA, 2007). A mathematical relationship has been developed between these two parameters to express HbA_{1c} values as average glucose concentration. The mathematical formula is as follows: Estimated Average Glucose (mmol/L) = (1.59 x HbA_{1c}) – 2.59 (Akinloye *et al.,* 2007).

2.5.3 Glycaeted Haemoglobin as an Indicator of Glycaemic Control

Over the past three decades, HbA_{1C} has been thought to represent the average level of glycaemia over the past six to eight weeks (Eric, 2000; Enzo and Jaako, 2011). It has also been shown that the glycation of haemoglobin occurs over the entire 120 days life span of red blood cell. However, it is pertinent to note here that recent glycaemia has the most significant influence on the HbA_{1C} value. Theoretical models have shown that a patient in stable control will have 50% of their HbA_{1C} formed in the month before sampling and 25% in the month before that and the remaining 25% in the two to four months before sampling(Eric, 2000; Enzo and Jaako, 2011).

Evidence now abound to show from the feasibility studies of Diabetes Control and Complications Trial (DCCT), which compared average multiple HbA_{1C} measurements to the average laboratory measured blood glucose profile over a period of one year, to show an excellent association (r= 0.80) (Eric, 2000). However, differences exists in individuals with a variation of about 2-4% in HbA_{1C} due to the fact that in the diabetic population, there is a proportion of people who appear to glycate haemoglobin at a faster rate or at a

slow rate than others. Recent data has now shown much of such differences can now be explained by the fact that high glycators tend to have red cells survive longer than slow glycators (cedeberg *et al*., 2010). Certainly other measures of determining glycaemic control other than glycaeted haemoglobin exist to date such as serum fructosamine, and 1, 5 anhydroglucitol, unfortunately, none of them has been extensively investigated like HbA_{1C}, and there are insufficient data to elucidate their comparison with glycaeted haemoglobin and therefore we cannot with certainty conclude that any of them can predict the risk of diabetes complications like HbA_{1C} does at the moment (Eric, 2000).

2.5.4 Glycaeted Haemoglobin for Diagnosis of Diabetes Complications

Two landmark studies, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Diabetes Prospective Study (UKPDS), set out to establish the effect of hyperglycaemia on microvascular complications of diabetes with type 1(insulin dependent) and type 2 (Non insulin dependent) diabetes, respectively (Eric, 2000). UPKDS (1998) studied progression of microvascular complications in the Japanese diabetic population.

2.5.5 Microvascular Complications of Diabetes Mellitus

The microvascular complications of diabetes include retinopathy, nephropathy and possibly neuropathy (WHO, 2011).

Diabetic Retinopathy

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for 10,000 new cases of blindness every year in the United States alone

(Fong *et al*., 2004). The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia (Fong *et al*., 2004). Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K. Prospective Diabetes Study (UKPDS), and most patients with type 1 diabetes develop evidence of retinopathy within 20 years of diagnosis (UKPDS, 1998; Keenan *et al.*, 2007). Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes (Fong *et al*., 2004). There are several proposed pathological mechanisms by which diabetes may lead to development of retinopathy (Fong *et al*., 2004).

Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway, this pathway involves the conversion of glucose into glucose alcohol (sorbitol) (Fong *et al*., 2004). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. In animal models, sugar alcohol accumulation has been linked to microaneurysm formation, thickening of basement membranes, and loss of pericytes. Treatment studies with aldose reductase inhibitors, however, have been disappointing (Gabbay, 1975; Fong *et al*., 2004; Gabbay, 2004).

Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs) (Gabbay, 2004). In animal models, these substances have also been associated with

formation of microaneurysms and pericyte loss, evaluations of AGE inhibitors are underway (Fong *et al*., 2004).

Oxidative stress may also play an important role in cellular injury from hyperglycemia. High glucose levels can stimulate free radical production and reactive oxygen species formation. Animal studies have suggested that treatment with antioxidants, such as vitamin E, may attenuate some vascular dysfunction associated with diabetes, but treatment with antioxidants has not yet been shown to alter the development or progression of retinopathy or other microvascular complications of diabetes (Kunisaki *et al*., 1995; Fong *et al*., 2004).

Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy (Aello *et al*., 1995; Fong *et al*., 2004; Keenan *et al.*, 2007).

Diabetic retinopathy is generally classified as either background or proliferative. It is important to have a general understanding of the features of each to interpret eye examination reports and advise patients of disease progression and prognosis (Watkins, 2003).

Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as “dots” and therefore are frequently referred to as “dot hemorrhages.” Hard exudates are caused by lipid deposition that typically occurs at

the margins of hemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. The appearance is one of grayish retinal areas. Retinal edema may require intervention because it is sometimes associated with visual deterioration (Watkins, 2003).

Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina ("cotton wool spots") can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial (Watkins, 2003).

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of renal failure in the United States. It is defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30-299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type 1 and type 2 diabetes (Gross *et al*., 2005).

As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes (Gross *et al*., 2005). In the European Diabetes Prospective Complications Study, the cumulative incidence of microalbuminuria in patients with type 1 diabetes was ~ 12% during a period of 7 years (Gross *et al*., 2005; Chaturvedi *et al*., 2011). In the UKPDS, the incidence of microalbuminuria was 2% per year in patients with type 2 diabetes, and the 10-year prevalence after diagnosis was 25% (Adler *et al*., 2003; Gross *et al*., 2005).

The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies), and other changes. The underlying mechanism of injury may also involve some or all of the same mechanisms as diabetic retinopathy (Gross *et al*., 2005).

Screening for diabetic nephropathy or microalbuminuria may be accomplished by either a 24-hour urine collection or a spot urine measurement of microalbumin. Measurement of the microalbumin-to-creatinine ratio may help account for concentration or dilution of urine, and spot measurements are more convenient for patients than 24-hour urine collections. It is important to note that falsely elevated urine protein levels may be produced by conditions such as urinary tract infections, exercise, and hematuria (Adler *et al*., 2003).

Initial treatment of diabetic nephropathy, as of other complications of diabetes, is prevention. Like other microvascular complications of diabetes, there are strong associations between glucose control (as measured by hemoglobin A_{1c} [A1C] and the risk of developing diabetic nephropathy. Patients should be treated to the lowest safe glucose

level that can be obtained to prevent or control diabetic nephropathy (DCCT, 1993; Adler *et al*., 2003; Gross *et al*., 2005). Treatment with angiotensin-converting enzyme (ACE) inhibitors has not been shown to prevent the development of microalbuminuria in patients with type 1 diabetes but has been shown to decrease the risk of developing nephropathy and cardiovascular events in patients with type 2 diabetes (Gross *et al*., 2005; HOPE, 2000).

In addition to aggressive treatment of elevated blood glucose, patients with diabetic nephropathy benefit from treatment with antihypertensive drugs. Renin-angiotensin system blockade has additional benefits beyond the simple blood pressure-lowering effect in patients with diabetic nephropathy. Several studies have demonstrated renoprotective effects of treatment with ACE inhibitors and angiotensin receptor blockers (ARBs), which appear to be present independent of their blood pressure-lowering effects, possibly because of decreasing intraglomerular pressure. Both ACE inhibitors and ARBs have been shown to decrease the risk of progression to macroalbuminuria in patients with microalbuminuria by as much as 60-70%. These drugs are recommended as the first-line pharmacological treatment of microalbuminuria, even in patients without hypertension (Gross *et al*., 2005).

Similarly, patients with macroalbuminuria benefit from control of hypertension. Hypertension control in patients with macroalbuminuria from diabetic kidney disease slows decline in glomerular filtration rate (GFR). Treatment with ACE inhibitors or ARBs has been shown to further decrease the risk of progression of kidney disease, also independent of the blood pressure-lowering effect (Gross *et al*., 2005).

Combination treatment with an ACE inhibitor and an ARB has been shown to have additional renoprotective effects. It should be noted that patients treated with these drugs (especially in combination) may experience an initial increase in creatinine and must be monitored for hyperkalemia. Considerable increase in creatinine after initiation of these agents should prompt an evaluation for renal artery stenosis (Rossing *et al*., 2003; Gross *et al*., 2005).

Diabetic Neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (ADA, 2007)." As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia, and some individuals may possess genetic attributes that affect their predisposition to developing such complications (ADA, 2007).

The precise nature of injury to the peripheral nerves from hyperglycemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy (Boulton *et al*., 2005). Because of the considerable morbidity and mortality that can result from diabetic neuropathy, it is important for clinicians to understand its manifestations, prevention, and treatment (Boulton *et al*., 2005).

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy in diabetes. Typically, patients experience burning, tingling, and "electrical" pain, but sometimes they may experience simple numbness. In patients who experience pain, it may be worse at night. Patients with simple numbness can present with a painless foot ulceration, so it is important to realize that lack of symptoms does not rule out presence of neuropathy. Physical examination reveals sensory loss to light touch, vibration, and temperature. Abnormalities in more than one test of peripheral sensation are >87% sensitive in detecting the presence of neuropathy. Patients also typically experience loss of ankle reflex (Boulton *et al*., 2005). Patients who have lost 10-g monofilament sensation are at considerably elevated risk for developing foot ulceration (Abbott *et al*., 2002).

Pure sensory neuropathy is relatively rare and associated with periods of poor glycemic control or considerable fluctuation in diabetes control. It is characterized by isolated sensory findings without signs of motor neuropathy. Symptoms are typically most prominent at night (Boulton *et al*., 2005).

Mononeuropathies typically have a more sudden onset and involve virtually any nerve, but most commonly the median, ulnar, and radial nerves are affected. Cranial neuropathies have been described but are rare. It should be noted that nerve entrapment occurs frequently in the setting of diabetes. Electrophysiological evaluation in diabetic neuropathy demonstrates decreases in both amplitude of nerve impulse and conduction but may be useful in identifying the location of nerve entrapment. Diabetic amyotrophy may be a manifestation of diabetic mononeuropathy and is characterized by severe pain and muscle weakness and atrophy, usually in large thigh muscles (Boulton *et al*., 2005).

Several other forms of neuropathy may mimic the findings in diabetic sensory neuropathy and mononeuropathy. Chronic inflammatory polyneuropathy, vitamin B_{12} deficiency, hypothyroidism, and uremia should be ruled out in the process of evaluating diabetic peripheral neuropathy (Boulton *et al.,* 2005).

Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death (Boulton *et al*., 2005). Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality (Maser *et al.,* 2003).

There is no specific treatment of diabetic neuropathy, although many drugs are available to treat its symptoms. The primary goal of therapy is to control symptoms and prevent worsening of neuropathy through improved glycemic control. Some studies have suggested that control of hyperglycemia and avoidance of glycemic excursions may improve symptoms of peripheral neuropathy. Amitriptyline, imiprimine, paroxetine, citalopram, gabapentin, pregablin, carbamazepine, topiramate, duloxetine, tramadol, and oxycodone have all been used to treat painful symptoms, but only duloxetine and pregablin possess official indications for the treatment of painful peripheral diabetic neuropathy (Boulton *et al.,* 2005).Treatment with some of these medications may be limited by side effects of the medication, and no single drug is universally effective. Treatment of autonomic neuropathy is targeted toward the organ system that is affected, but also includes optimization of glycemic control (Boulton *et al.,* 2005).

The UKPDS (1998) group published their data buttressing the fact that HbA_{1C} could be used in predicting the risk of developing small vessel complications in type 2 DM patients. The UKPDS involved 3,867 older subjects (mean age 54 years) who were either assigned to the intensive treatment with an aim to remain free of glycaemic symptoms and/or keep the fasting blood glucose below 15mmol/l with measurement of HbA_{1C} again as the corner stone of treatment evaluation, Still a 25% risk reduction in microvascular complications was observed (Eric, 2000; UKPDS, 1998). UKPDS showed that hyperglycaemia as measured by HbA_{1C} is not the sole contributor to the risk of microvascular complications. For example, a reduction in blood pressure from 154/87mmHg to 144/82 mmHg was found to be associated with 37% decrease in microvascular endpoints (Eric, 2000). Another landmark study is the Kumamoto Study, which was a randomized clinical trial designed to compare intensive insulin therapy using multiple insulin injections with conventional insulin injection therapy to evaluate the effects on the development and progression of microvascular complications in Japanese patients with type 2 diabetes (David *et al*., 2014). Observations also made from the trial showed 7.7% of the subjects on the MIT group progressed to retinopathy while 32% on the CIT group progressed to retinopathy, as well as 11.5% to 43.5% for nephropathy respectively, and a similar value was obtained for neuropathy (David *et al*., 2014).

2.5.6 Macrovascular Complications of Diabetes Mellitus

Macrovascular complications remain the major cause of morbidity and mortality in diabetes mellitus (Eric, 2000). Diabetes is associated with a two to three fold increased risk of coronary heart disease in men and four to five fold in premenopausal women (Eric, 2000). It is worthwhile to note that both the DCCT trial and the UKPDS did not set out

primarily to establish whether a relationship exist between HbA_{1c} and heart disease but subgroup analysis has shown that in the DCCT study, the cardiovascular event rate waslow presumably because of the age of the patients recruited, but there was still an excess of macro-vascular complications in the conventional group [40 vs 23] (Eric, 2000). In the UKPDS, however, the event rate was higher, but the HbA_{1c} appears to give an indication of macrovascular risk (additional to other factors; hypertension, smoking e.t.c) in patients with diabetes (Eric, 2000). The Kumamoto study in the Japanese with type 2 DM also showed that the total events of cardiovascular, cerebrovascular, and peripheral vascular diseases in the CIT group occurred twice as much as those in the MIT group (1.3 vs. 0.6 events/100 patient-years) (Eric, 2000).

In a recent study by Elizabeth *et al*. (2010) a study involving 1,062 black and whites adult who didn't have history of diabetes or cardiovascular disease between 1990 -1992 of the Atherosclerosis risk in adjusted communities (ARIC) study found a multi variable adjusted ratios of HbA_{1C} of 6.5% and above for newly diagnosed diabetes with 95% confidence interval of 1.95 (1.53 to 2.48) 1.00 reference. The hazard ratios for stroke and coronary heart disease were similar. They therefore suggested that glycaeted haemoglobin was similarly associated with a risk of diabetes and more strongly associated with the risk of cardiovascular disease and death from any cause as compared with fasting blood glucose (Elizabeth *et al*., 2010). Their data supports the use of glycaeted haemoglobin for the diagnosis of diabetes mellitus.

2.6 ALBUMINURIA

Microalbuminuria is defined as levels of albumin ranging from 30 - 300 mg in a 24-h urine collection (ADA, 2007). Albuminuria is a well-known predictor of poor renal outcomes in patients with type 2 diabetes and in essential hypertension (Mogense, 1984; Chawta *et al*., 2009). Albuminuria has also been shown more recently to be a predictor of cardiovascular outcomes in these populations (Anavekar *et al*., 2004; Ibsen *et al.,* 2004). There is emerging data that reduction of albuminuria leads to reduced risk of adverse renal and cardiovascular events (Brenner, *et al.,* 2001; Ibsen, *et al., 2004*). It has become increasingly clear that albuminuria should not only be measured in all patients with type 2 diabetes and hypertension, but also steps should be taken to suppress albuminuria to prevent future renal and cardiovascular adverse events (Brenner, *et al.,* 2001; Ibsen, *et al., 2005*).

2.6.1 Measurement of Microalbuminuria

Measuring urinary albumin excretion by dipstick without simultaneously measuring creatinine is subject to false negative and false-positive results due to variations in urine concentration caused by hydration level (ADA, 2010). Although urinary dipsticks are acceptable for quick screening, other more precise measurements should be done to quantify urinary albumin excretion rates [AERs], (ADA, 2010). Albuminuria can be measured in several ways: *1*) measurement of albumin-to creatinine ratio (ACR) in a random or first morning spot collection, *2*) 24-h urine collection with measurement of creatinine to verify adequacy of the collection, and *3*) timed (4-h or overnight) urine

collections (ADA, 2010). Although the 24-h urine collection would overcome issues of diurnal variation in albumin excretion, it is subject to collection errors. The Kidney Disease Outcomes Quality Initiative (KIDOQI) guidelines state that ACR measurement in a first-morning spot urine collection is adequate and a timed urine collection is not necessary (KIDOQI, 2002). However, because women excrete less creatinine than men and microalbuminuria is based on a fixed amount of urinary albumin excretion per day, the definitions of microalbuminuria are different in men and women when using ACRs (Connell, et al., 1994). Microalbuminuria was first defined by Mogensen (1984) and others as 30–300mg urinary albumin excretion per 24 h. However, at the time, there was not widespread use of inhibitors of the renin angiotensin system. As noted below, inhibition of the renin angiotensin system decreases urinary albumin excretion, and drugs to inhibit the renin angiotensin system are currently in wide use. A patient being treated with drugs that inhibit the renin angiotensin system, with urinary albumin excretion of 30–300 mg per 24 h, would have likely had much higher levels of AER without such drugs when Mogensen first defined microalbuminuria (Mogensen, 1984). Hence, most patients who have urinary albumin excretion in the microalbuminuria range currently have more advanced disease than patients in the past. In addition, microalbuminuria and albuminuria or proteinuria are part of a clinical continuum of risk and prognosis (Basi, 2008).

2.6.2 Albuminuria and Renal Outcomes in Type 2 Diabetes

There have been several studies examining the relationship between microalbuminuria and renal outcomes in type 2 diabetes. Mogensen (1984) studied the predictive value of microalbuminuria in patients with type 2 diabetes. It was predictive of the development of

overt proteinuria as well as mortality. Patients with type 2 diabetes and albumin concentrations of 30–140 g/ml at baseline were more likely to develop clinically detectable proteinuria (400g/ml) after 9 years of average follow-up than patients with baseline urinary albumin concentrations 30 g/ml. These findings were supported by Berrut *et al.* (1997), who examined patients with type 2 diabetes and hypertension. The GFR of patients with microalbuminuria declined more than the GFR of patients with normoalbuminuria over the average 22 months of follow-up. There have also been several larger trials that have shown the association between albuminuria and renal outcomes in patients with type 2 diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT) examined 1,715 patients with hypertension, type 2 diabetes, and proteinuria. Patients enrolled in IDNT had urinary protein excretion of at least 900 mg/24 h and serum creatinine concentration between 1.0 and 3.0 mg/dl in women and 1.2 and 3.0 mg/dl in men at baseline (Lewis *et al.,* 2001). The risk for the development of end-stage renal disease or doubling of serum creatinine during the average 4 years of follow-up doubled for each doubling of baseline proteinuria level (hazard ratio [HR] (Atkins *et al*., 2005). Similarly, the Reduction of Endpoints in Non-Insulin Dependent, Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study followe1,513 patients with type 2 diabetes and nephropathy (Brenner *et al*.,2001). Nephropathy was defined as a urinary ACR 300 mg/g with a serum creatinine level of 1.3–3.0 mg/dl. The presence of albuminuria was associated with an adjusted HR of 6.2 for the outcome of doubling of serum creatinine or end-stage renal disease (Atkins *et al*., 2005). Atkins *et al*. (2005) have demonstrated that microalbuminuria is a potent risk factor for the development of progressive kidney disease. It portends the future development of overt proteinuria, doubling of serum creatinine, end- stage renal disease, and mortality (Atkins *et al*., 2005).

Several studies have shown that reduction of albuminuria by inhibition of the renin-angiotensin aldosterone system is associated with the preservation of renal function (Atkins *et al*., 2005). The use of angiotensin receptor blockers (ARBs) is clearly beneficial in reducing proteinuria, and this is associated with improving renal outcomes. In addition, increasing the dose of ARB has been found to have greater renoprotection, independent of blood pressure control. The Irbestartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study, which compared 150 and 300 mg irbesartan daily to placebo in 590 hypertensive patients with type 2 diabetes and microalbuminuria found the hazard ratio for progressing to overt nephropathy (urinary albumin excretion rate in an overnight specimen 200 g/min and at least 30% higher than the baseline rate on at least two consecutive visits) was 0.56 in the 150 mg group and 0.32 in the 300 mg group (Parvin *et al.,*2001). This was after adjustment for the baseline level of microalbuminuria and the blood pressure achieved during the study. Given the improvement in outcomes with higher doses of ARBs, there is now interest in whether doses beyond the current recommended dosage levels may provide increased RAAS (Basi, 2008).

The Microalbuminuria Reduction with Valsartan (MARVAL) trial administered 80 mg/day valsartan or 5 mg/day amlodipine to 332 patients with type 2 diabetes and microalbuminuria (49) (Basi, 2008). The urinary albumin excretion rate at 24 weeks was 56% of baseline with valsartan and 92% of baseline with amlodipine (Basi, 2008).

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY AREA

The study was conducted in Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH) in Bauchi. Bauchi is the capital city of Bauchi State, and is located on the northern edge of the Jos plateau, at an elevation of 616 m. Bauchi local government covers an area of 3,687 km^2, at 10^0 18' 57" N and 09^0 50' 39" E. Bauchi has tropical savanna climate, abbreviated "AW" on climate maps. The hospital bed space capacity is 650. The average attendance at the diabetic clinic is 100 patients every clinic day (about 800 patients per month), coming mainly from the city and its environs.

3.2 STUDY POPULATION

The study population were male and female patients with type 2 diabetes mellitus aged 30-65years, attending the diabetic clinic of the hospital. Age and sex matched controls were selected from other non-diabetic (from Hypertensive clinic) patients in the hospital.

3.3 SAMPLE SIZE EXTIMATION

The minimum sample size for the study shall be estimated using the Lowenga formular below:

$n = Z^2pq/d^2$

Where, n = minimum sample size; Z = standard normal deviate at 95% confidence interval, i.e. 1.96; *p* = prevalence rate (from past study) i.e. prevalence of vascular

complications among type 2 diabetes mellitus patients. According to Litwak *et al.* (2013) prevalence of microvascular complication is 0.37 (37%), so,

p = 0.37; q = complimentary probability of p, i.e. q = (1-p) = 0.63; and d = precision (margin of error) at 95% confidence limit, standard value 0.05.

Substituting the above values in the formula, we get

$n = (1.96^2 x 0.37 x 0.63)/0.05^2 = 358$

The sample size was rounded to 360 to increase the accuracy of the results. A similar number of matched non-diabetic persons will be used as controls.

3.4 STUDY DESIGN AND SAMPLE SELECTION

The study design used was case control. Consecutive patients diagnosed with type 2 diabetes mellitus attending the clinic were recruited up to the desired number.

3.4.1 Inclusion Criteria

Male and female patients aged 30-70yrs with type 2 DM, irrespective of duration of diagnosis and treatment, attending diabetic clinic of the hospital were eligible for study. Other non- diabetic patients (from Hypertensive clinic) in the hospital were selected as controls.

3.4.2 Exclusion Criteria

Type 1 DM patients and type 2 DM aged below 30 years were excluded. Patients with already diagnosed renal disease not related to DM were also excluded. Patients with CCF,

on ACE inhibitor (anti Hypertensive drugs), UTI, Haemoglobinopathies, pregnant women were all excluded.

3.5 DATA COLLECTION INSTRUMENT AND PROCEDURE

3.5.1 Instrument of Data Collection

The data was collected using a structured interviewer-administered questionnaire. Data collected include complete biodata (Name, age, sex, marital status, region, religion and occupation) socio–demographic and athropometric characteristics, clinical history including all complications such as hypertension, symptoms of renal failure, retinopathy, peripheral neuropathy and visual disturbances.

3.5.2 Data and Sample Collection Procedure

The procedure for data collection was explained to the subjects by the researcher. After administration of the questionnaire, blood and urine samples were collected from each subject for subsequent laboratory analyses by the researcher and assistant. Five milli litre of blood were taken after over-night fasting of 8-12h to measure fasting plasma glucose and glycaeted haemoglobin (HbA_{1c}). Also, a midstream early morning urine was used to measure micro- albuminuria. Subject's heights and weights were determined to estimate the body mass index (weight divided by height square). Body mass index 18-25 kg/m^2 was considered as normal (ADA, 2011). Blood pressure was measured with the aid of a Mercury Sphygmomanometer on the right upper arm in the sitting position after at least 10 minutes of rest. Patients were categorized as hypertensive if the systolic blood pressure is $\geq$ 130 mm Hg and/or diastolic blood pressure was $\geq$ 85 mm Hg (ADA, 2010).

3.6 LABORATORY ANALYSES

3.6.1 Measurement of Albuminuria

The procedure was conducted as described ealier (Miltons Keynes primary care trust, 2007). Briefly, a clean container was provided. Each container was numbered and dated as appropriate. Urine sample was collected inside the container. Microalbustix strip was carefully dipped into the urine sample and allowed to soak, while holding the other end. The microalbustix strip was removed. The color change on the strip was observed within 5 to 10 seconds. The color change was compared with that of pre-programmed calibration algorithm provided on the microalbustix strip container. The corresponding colour changes indicated the presence or absence of microalbuminuria.

3.6.2 Measurement of Glycaeted Haemoglobin

The subject's finger tips were cleaned with cotton wool and spirit and allowed to dry. A prick was made using a lancet. Blood sample (5µl) was squeezed and dropped onto R1 reagent (Boronic acid conjugate (blue), which lysed erythrocytes, precipitate hemoglobin, couple colored compound to the glycaeted part of the haemoglobin). The reagent(R1) was dropped on a test cartridge, second reagent (R2)/ washing solution was added to same test cartridge and then inserted into the machine (Quo lab HbA1c analyser) and allowed for 4 minutes. The values were displayed on the screen as percentage.

3.7 OTHER MATERIALS USED IN THE STUDY

The following instruments and materials were used: glycaeted hemoglobin measuring machine (Quo labHbA_{1c} analyser, EKF lab Inc., UK), microalbuminuria strip (Microalbustix, Siemen health care diagnostic ltd, UK), glucometer (On call^{R} plus, Alcon lab Inc., USA), test tubes, sphigmo manometer (Accusson, Decamet MSK ltd, England), weighing/standiometer machine (Hamason, Echukson ltd, China), measuring tape (Tapemeter, Habric ltd, China).

3.8 LIMITATIONS OF THE STUDY

The number of patients attending the diabetic clinic of the hospital was relatively low compared to the sample size needed for the study. As a result majority of the patients were recruited into the study and most of them were females. Hence, the number of females was much higher than males in both the diabetic and control groups. Inspite of this, the two groups were matched for sex, the ratio of males: females for the two groups were similar.

3.9 ETHICAL CONSIDERATIONS

Ethical approval was obtained from review board of ATBUTH. Signed informed consent was obtained from each subject before the commencement of data collection. The study was strictly conformed to the provisions of the declaration of Helsinki as revised in Tokyo in 1975 (WHO, 2001).

3.10 STATISTICAL ANALYSES

Data were collated and analysis done using the statistical package for social sciences (SPPS) program for windows version 20.0 (SPSS Inc., Chicago, IL). Quantitative data was expressed as mean ± S.E.M. and compared using independed sample t- test. The two groups were compaired for difference in retinopathy using Mann-Whitney u test. Chi-square test was used to determine association between categorical variables. P values < 0.05 were considered significant.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 RESULTS

4.1.1 Socio-demographic Characteristics of Diabetic and Non-diabetic Control.

The socio-demographic data obtained were as presented in table 4.1. Mean age was 49.61 ± 0.50 and 51.92 ± 0.48 years for diabetic and control groups, respectively. There is no significant difference in age between the two groups ($P > 0.05$). The number of females who participated in the study (455) was about 2.4 times the number the number of males (188), and the ratio was similar for the diabetic and control groups.

Table 4.1: Socio – Demographic Characteristics of Diabetic and Control Subject who Participated in the Study.

Characteristics		**Diabetic**	**Control**	**Total**
Age	30 -50 years	152(58.2%)	162(42.4%)	314
	50-70 years	109(41.8%)	220(57.6%)	329
	All ages	261(100%)	382(100%)	643
Sex	Male	101(32.2%)	87(26.4%)	188
	Female	213(67.8%)	242(73.6%)	455
	All sexes	314(100%)	329(100%)	643
Religion	Islam	273(87%)	282(85.7%)	555
	Christianity	41(13%)	47(14.3%)	88
	All religion	314(100%)	329(100%)	643
Marital status	Single	5(1.6%)	9(2.7%)	14
	Married	271(86.5%)	268(81.5%)	539
	Divorce	6(1.9%)	19(5.8%)	25
	Widow	32(10.0%)	33(10.0%)	65
	All types	314(100%)	329(100%)	643
Employment status	Gov. employed	51(16.2%)	77(23.4%)	128
	Self employed	47(14.9%)	90(27.4%)	137
	Privet Sect. empl.	3(1.1%)	0	3
	Unemployed	213(67.8%)	162(49.2%)	375
	All types	314(100%)	329(100%)	643
Level of Education	Secondary cert.	90(28.7%)	82(24.9%)	172
	Diploma	49(15.6%)	56(17.0%)	105
	Degree	18(5.7%)	39(11.9%)	57
	Masters	8(2.6%)	0(0%)	8
	Qur'anic	94(29.9%)	109(33.1%)	203
	None	55(17.5%)	43(13.1%)	98
	All types	314(100%)	329(100%)	643

4.1.2 Signs and Symptoms of Diabetic Complications among Diabetics and Controls.

Table 4.2 shows the frequency of different symptoms and signs of diabetic complications among the diabetics and controls. Mean BMI was 26.42 ± 0.18 and 26.55 ± 0.13 for diabetics and controls, respectively. The difference in mean BMI between the two groups was not significant (P <0.05), There was significant difference (P < 0.01) in retinopathy between the diabetic and control groups.

Table 4.2: Frequency Distribution of Symptoms and Signs of Diabetic Complications In Diabetic and Non- diabetic Control Subjects.

Symptoms and signs		Diabetics	Control	Total
Duration of diagnosis	0	0(0%)	329(100%)	329
	< 1yr	16(5.1%)	0	16
	1 - 5yrs	172(54.8%)	0	172
	5 – 10yrs	104(33%)	0	329
	>10 yrs	22(7.1%)	0	22
	All	314(100%)	329(100%)	643
Family history of DM	Yes	230(73.2%)	7(2.1%)	237
	No	84(26.8%)	322(97.9%)	406
	All	314(100%)	329(100%)	643
Decreased urine volume	Yes	141(44.9%)	3(0.9%)	144
	No	173(55.1%)	326(99.1%)	499
	All	314(100%)	329(100%)	643
Visual problem	Yes	197(62.7%)	32(9.7%)	229
	No	117(37.3%)	297(90.3%)	414
	All	314(100%)	329(100%)	643
Fundoscopic findings	Not Applc.	48(15.3%)	89(27.7%)	137
	Grade 1	91(29.0%)	100(30.4%)	191
	Grade 2	121(38.5%)	87(26.4%)	208
	Grade 3	52(16.6%)	49(14.9%)	101
	Grade 4	2(0.6%)	4(0.6%)	6
	All	314(100%)	329(100%)	643
Body Mass Index	Normal	110(35.1%)	96(29.2%)	206
	Over weight	175(55.7%)	205(62.3%)	380
	Obese	29(9.2%)	28(8.5%)	57
	All	314(100%)	329(100%)	643

Key (BMI)

Normal (18-24.9) kg/m^2

Overweight (25-29.9) kg/m^2

Obesed (> 30)kg/m2

4.1.3 Micro-Albuminuria among Diabetics and Non-Diabetic Controls.

Figure 4.1 shows the frequency distribution of micro-albuminuria among diabetics and controls 30.9% and 17.6% of subjects had micro-albuminuria among the diabetics and controls, respectively. While 69.1% and 82.4% had no micro-albuminuria among diabetics and controls, respectively.

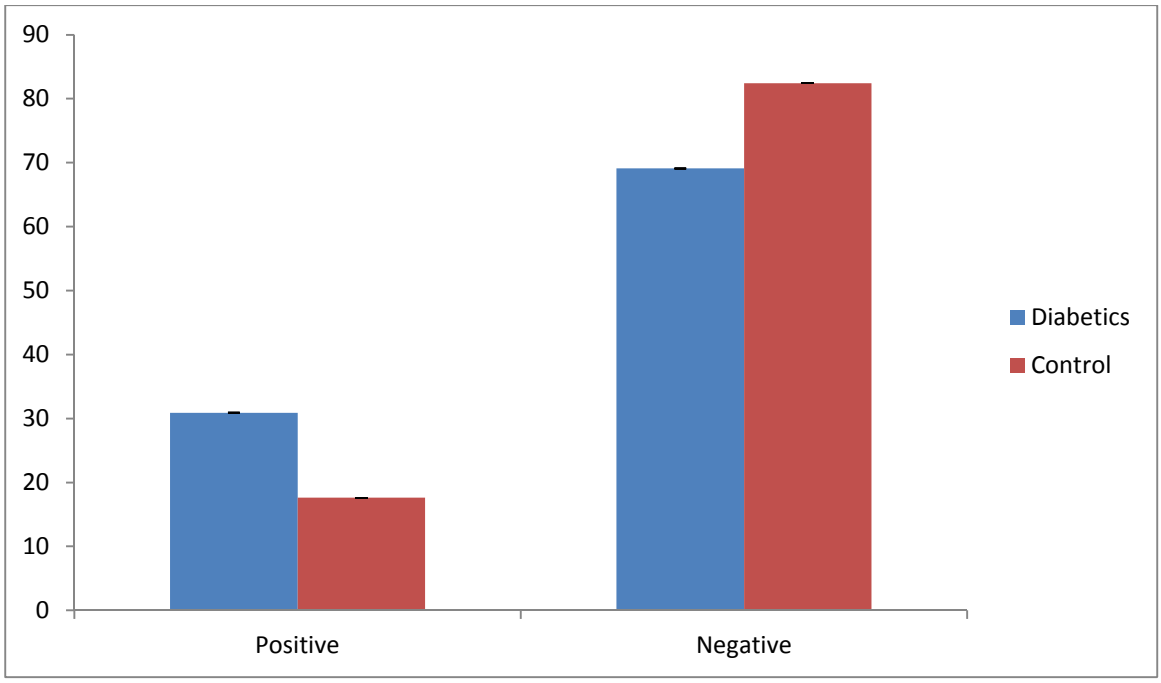

Figure 4.1: Frequency distribution of micro- albuminuria among diabetic and non-diabetic control subjects.

4.1.4 Level of Glycaeted Haemoglobin among Diabetics and Non-Diabetic Controls.

The frequencies of normal and abnormal levels of HbA1c among the two groups is shown in figure 4.2. Mean glycaeted haemoglobin was 6.67 ± 0.04% and 5.00 ± 0.03% for diabetics and controls, respectively. There was a significant difference ($P < 0.01$) in the level of HbA1c between the diabetic and control groups.

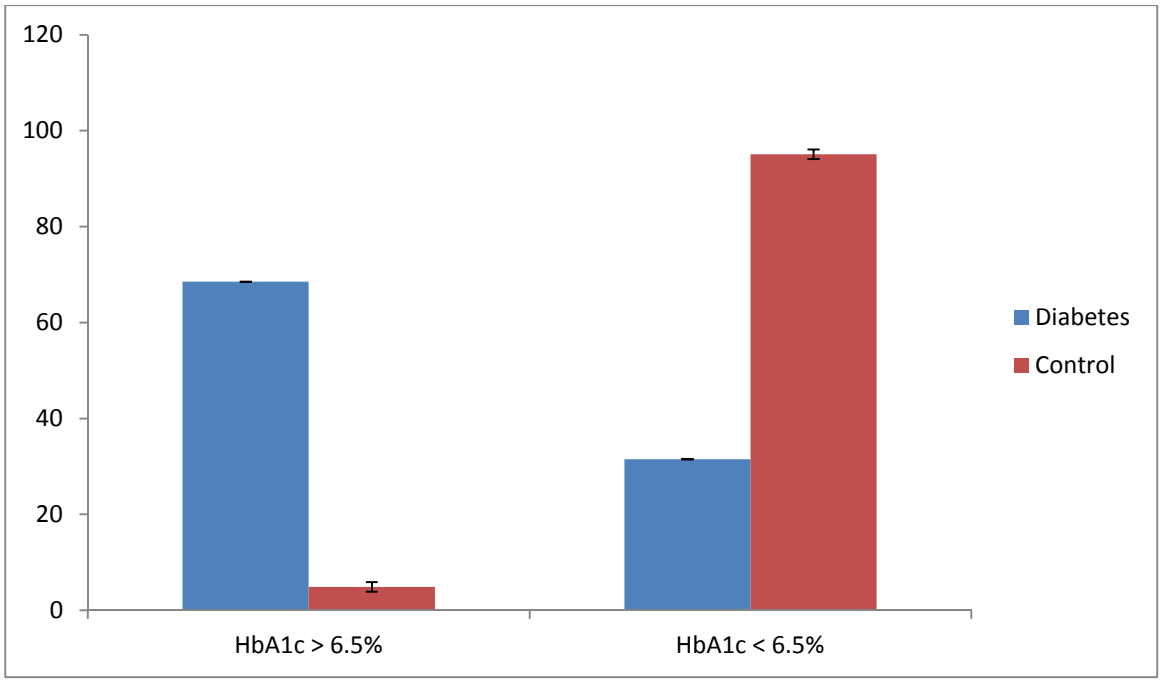

Figure 4.2: Frequency of abnormal (> 6.5%) and normal (< 6.5%) levels of glycaeted haemoglobin among the two groups, diabetic and control subjects.

4.1.4 Level of Fasting Blood Glucose among Diabetic and Non-Diabetic Controls In a Study of Level Micro-Albuminuria and Glycaeted Haemoglobin

Figure 4.3 shows the frequency distribution of normal and abnormal FBG among the diabetics and controls. Mean FBG was 10.13 ± 0.023 and 4.38 ± 0.05(mmol/l) for diabetic and controls, respectively. There was a significant difference ($P < 0.01$) in FBG between the two groups.

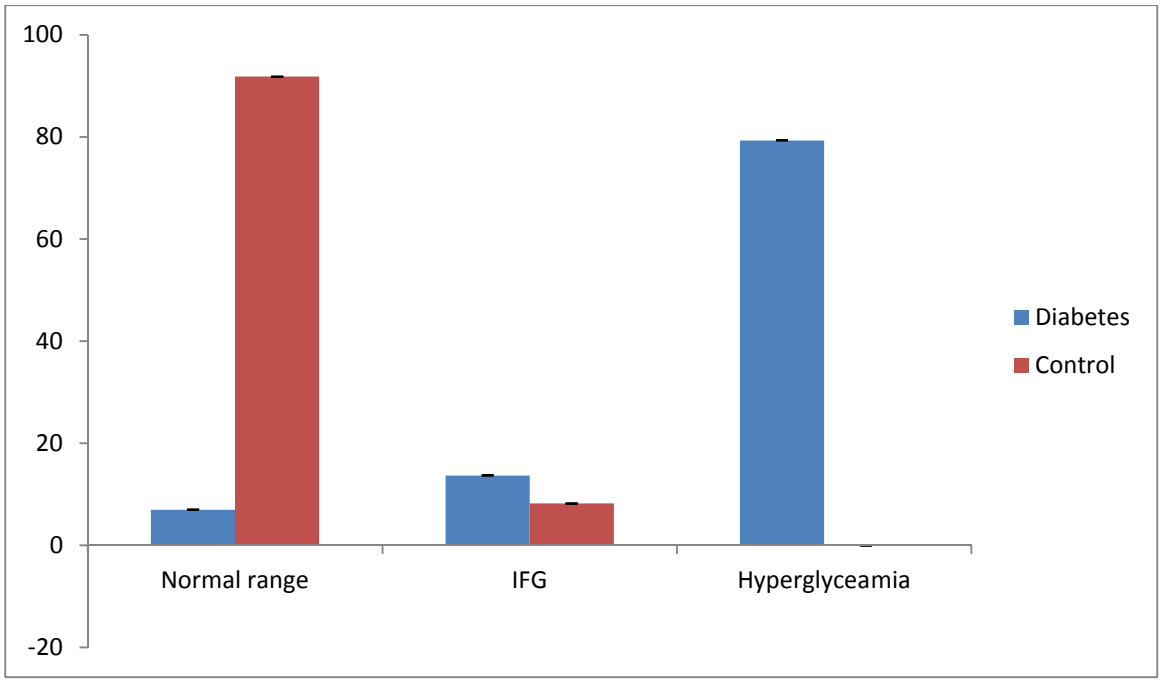

Figure 4.3: Frequency Distribution of normal and abnormal of blood glucose levels among diabetic and control subjects.

Key (FPG)

Normal range- 3.5- 6.0mmol/l

Impaired Fasting Glucose- 6.1- 6.9mmol/l

Hyperglycaemia- >7mmol/l

4.1.5 Relationship Between Micro-Albuminuria and Some Selected Complications

There was no association between micro – albuminuria (30.9%) and decreased urine volume ($P > 0.05$) and visual disturbance ($p>0.05$). However, there was an association between micro – albuminuria and retinopathy ($p < 005$).

4.1.6 Relationship Between Glycaeted Haemoglobin and Some Selected Complications

There was no association between glycaeted haemoglobin(6.67± 0.04) and decreased urine volume ($P > 0.05$), visual problems ($P > 0.05$), and retinopathy ($P > 0.05$).

DISCUSSION

4.2 DISCUSSION

The Study investigated microalbuminuria and glycaeted haemoglobin among type 2 diabetese patients attending a tertiary health institution in Bauchi, North East Nigeria. The age range of the participants was 30–70 years. The case control study had two groups- diabetic and non-diabetic control groups which were matched for age and sex. However, there were more females than males in both the diabetic and control groups. This could be explained due to the fact, that there are generally more female than male patients attending the hospital.

There was higher percentage of patient with microalbuminuria among the diabetic (30.9%) compared to the non-diabetic controls (17.6%). Microalbuminuria is the result of destruction of glomerular capillary basal membrane leading to escape into urine of large molecular size proteins like albumin (Kumar and Clark, 2012). This finding is in agreement with previous ones (Kundu *et al*., 2013; Stephane *et al*., 2013; Xiaolin *et al;* 2015). Serum level of glycaeted haemoglobin was within the physiological limits (<6.5 %) for the non-diabetic controls. For the diabetic group, glycaeted haemoglobin of 6.67 % was higher than what was detected in the control and fell above the normal range. The level of HbA1c has been widely accepted as an indicator of mean daily blood glucose concentration over the preceeding 8-12 weeks, This signifies relatively poor glycaemic control over this period preceeding the study. This result is in keeping with several others reported in the past (ADA, 2011; WHO, 2011; Naveen *et al.,* 2012; Kundu *et al*., 2013). The evidence of poor glycaemic control reported corroborates the other finding of

microalbuminuria, which is a consequence of glycaetion of membrane proteins leading to their malfunction.

There was significant hyperglycaemia among the diabetese (FBG = 10.13 ± 0.023mmol/l) compaired with non –diabetic controls who had normal levels of (FBG = 4.38 ± 0.05mmol/l).This provides additional support for the abnormal level of glycaeted haemoglobin reported among the diabetics in this study. This finding agrees with others reported earlier (Cederberg *et al.,* 2010; Huang *et al.,* 2011; Wang *et al.,* 2011). BMI was within the overweight range and was similar for the two groups. Indeed, a BMI of 26 was quite close to normal and could be the result of modification of lifestyle (appropriate diet modifications and exercise, though not included in our questionaire) following patient education during clinic visits.

Retinopathy was significantly higher among the diabetics compaired to the controls. This result indicates that diabetes is a risk factor for retinopathy and is in line with other findings above in support of microvascular complication. The results agree with report of (David *et al.,* 2014).

Based on the findings of this study, there was an association between micro-albuminuria and retinopathy ($p < 0.05$). This means that a diabetic patient, who has one of the signs, is likely to have the other. However, there was no association between micro-albuminuria and visual disturbance *per se*. This may be probably because many of the patients may not complain of visual problems during the early stages of retinopathy (grade 1 retinopathy). There was also no association between microabuminuria and decreased urine volume. Again, decreased urine volume (as a symptom, not a sign) may go undetected by the

patient during early stages of renal failure, these study is in keeping with many other studies (Lunnetta *et al.,* 1998; Sobngwi *et al*., 1999*;* Manaviat *et al*., 2005).

There was no association between glycaeted haemoglobin with any of decreased urine volume, visual problems and retinopathy. Pathophysiologically, abnormally high glycaeted haemoglobin will preceed microalbuminuria.

Hence, it is conceivable, that while microalbuminuria is associated with only one of the three complications examined (above), raised serum glycaeted haemoglobin is not associated with any of them, in keeping with some studies (Ozmen and Boyvada, 2003; Santos *et al*., 2005).

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 SUMMARY

The aim of the study was to determine the level of micro-albuminuria and glycaeted haemoglobin in patients with type 2 diabetes mellitus, and its relationship with some selected diabetic complications.

The level of microalbuminuria was tested using Micral test strip, and glycaeted haemoglobin using Quo Laboratory glycaeted haemoglobin machine. Microalbuminuria level among diabetic was 30.9% and that of control 17.6%, while abnormal levels of glycaeted haemoglobin (> 6.5%) among diabetic was 68.5%, and that of control was 4.9%. Micro-albuminuria (30.9%) was not associated with decreased urine volume and visual disturbance. There was significant association between micro – albuminuria and retinopathy. Glycaeted haemoglobin was no association decreased urine volume, visual disturbance and retinopathy. It was concluded that the prevalence of microalbuminuria was high among diabetics compared to non-diabetic controls. Level of serum glycaeted haemoglobin was abnormally high among diabetics, when compared to non-diabetic controls.

5.2 CONCLUSION

Based on the findings in this study, the following conclusions were drawn:

1. The level of microalbuminuria is high among diabetics compared to non-diabetic controls.
2. Levels of serum glycaeted haemoglobin and FBS were abnormally high among diabetics, when compared to non-diabetic controls.
3. Retinopathy, visual disturbance and decreased urine volume were found to be prevalent among diabetics compared to non diabetic controls.
4. Microalbuminuria was associated with retinopathy, but not with visual problems and decreased urine volume.While high glycaeted haemoglobin levels were not associated with any of retinopathy, visual problem and decreased urine volume.

5.3 RECOMMENDATION

1. All diabetic patients should be screened early and routinely for microalbuminuria and glycaeted haemoglobin for early intervention to prevent microvascular complications.
2. Fundoscopy is recommended for all diabetic patients with microalbuminuria in order to diagnose and manage retinopathy.

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Appendix I

QUESTIONNAIRE

Dear respondent,

I would be grateful if you can spare some time to answer the following questions on my research to determine the prevalence of microalbuminuria, glycaeted hemoglobin and diabetic complications among patients attending this hospital. Kindly answer the following questions as honestly as you can. I sincerely promise to treat all information confidential.

SECTION A: BIODATA

1) Code number: […….]

2) Age:

3) Sex: Male [ ] Female [ ]

4) Marital Status: Single [ ] Married [ ] Divorced [ ] Widowed [ ]

5) Religion: Islam [ ] Christianity [ ] No religion [ ]

6) What is your type of employment/occupation?

Government employed [ ] Self employed [ ] Private sector employed [ ] Unemployed [ ]

If employed, what type of job do you do? ……..

7) Level/Type of education:

GCE/SSCE[ ] Diploma [ ] Degree[ ] Masters Degree[ ] Quranic [ ] None[ ]

SECTION B: CLINICAL HISTORY

1) Duration of diagnosis: < 1yr [ ] 1-5yrs [ ] 5-10yrs [ ] > 10yrs [ ]

2) Duration of treatment: < 1yr [ ] 1-5yrs [ ] 5-10yrs [ ] > 10yrs [ ]

3) Type of treatment: Oral hypoglycemic [ ] Oral hypoglycemic + Insulin [ ]

4) Family history of diabetes: Yes [ ] No [ ]

5) Decrease urine volume: Yes [ ] No [ ]

6) Eye problem /visual blurring: Yes [ ] No [ ]

7) Genital thrush: Yes [ ] No [ ]

8) Recurrent vaginal discharge: Yes [ ] No [ ]

9) Tingling sensations: Yes [ ] No [ ]

10) Chest pain: Yes [ ] No [ ]

11) Do you usually experience difficulty achieving erection? Yes [ ] No [ ]

12) Have you ever had weakness of one side of the body? Yes [ ] No [ ]

13) Are you hypertensive? Yes [ ] No [ ]

14) Duration of the hypertension: <5 yrs [ ] 5-10 yrs [ ] >10 yrs [ ]

15) How often did you miss your medication in the last 5 years?

Never [ ] 1 in 6 months [ ] 1-2 in 1 month [ ] 1 in 1 week [ ]

SECTION C: PHYSICAL EXAMINATION

1) Weight:

2) Height:

3) Body mass index (weight/Height2):

4) Blood pressure:

5) Fundoscopy:

Appendix II

Informed consent form

I---------- here by declare that the procedure involved in carrying out this research work, the confidentiality of the information I will give, the option of opting out at any stage of the interview and the importance of the research in improving health was thoroughly explained and understood by me. I therefore agreed to be selected as a subject for this research.

Sign---------- Date ----------

Appendix III

ETHICAL APPROVAL

Appendix IV

STUDY BUDGET

Number of participants 720.

Estimated coast of the Study

1- Two number of Accoson^{R} sphygmomanometer at …….N 21,200

2- Two number of Hanson ^{R} weighing scales at…….. N 14,350

3- Two stature meter at…… N 14,100

4- 24 packs of micral test strips(Micro-albuminuria) each N7650….....N 183,600

5- Seven hundred and fifty number of urine sample bottles at N50…..……..N 37,500

6- Two number of littmans stethoscope at ……N20,000

7- One Computer at…… N120,000

8- Six copie of Proposal book at N 500 each…….…….. N 30

9- Seven hundred and fifty pairs of surgical gloves at N100 each…..……..... N 75,000

10- Seven hundred and fifty copies of Questionnaire at N30 each……..……N 22,500

11- Seven hundred and fifty copies of consent form at N 10 each…….…….....N 7,500

12- Fasting glucose estimation of 750 samples at N150 each…….……N112, 500

13-Glycaeted haemoglobin assay for 750samples at N1000……N750, 000

14- Logistics to cover for the transport and training of five assistants..…….N 50,000

TOTAL…….1, 428,550