PREVALENCE OF TYPE 2 DIABETES MELLITUS IN UNIVERSITY OF NIGERIA NSUKKA STAFF QUARTERS

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CHAPTER ONE

1.1: BACKGROUND TO THE STUDY

The incidence and prevalence of diabetes mellitus (DM) has continued to increase globally with the resulting burden resting more heavily on tropical, developing countries.[1,2]As the developing world urbanizes and becomes more affluent, so the incidence of type 2 diabetes mellitus rises.[3] This has brought up an increase in worldwide prevalence of diabetes so much that it has become a common problem in many ethnic groups that previously were hardly affected. The progressive increase in the prevalence rates of diabetes is associated with lifestyle changes; overweight and obesity, physical inactivity, alcohol consumption, dietary changes and cigarette smoking- factors that are potentially modifiable.

Diabetes mellitus is a group of metabolic disorder characterized by an underlying hyperglycemia (resulting from absolute or relative lack of insulin) with nephropathy, neuropathy, angiopathy and occulopathy as its attendant complications. Obesity, diet and sedentary life style have been named as the major causative factors for the prevalence of the disease. Type 2 DM, which is the commonest of two basic types of DM, is increasingly being recognized in relatively young persons, due to the high prevalence of environmental and genetic risk factors.[2]

People living with type 2 DM are more vulnerable to varied forms of both short- and long-term complications, which often lead to their premature death. This vulnerability to increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Nigeria.[3,4] It is predicted that prevalence of DM in adults will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64.[5] With the current trend of transition from communicable to non-communicable diseases, it is projected that the latter will equal or even exceed the former in developing nations, thus culminating in double burden.[6,7]

A seemingly uncomplicated diabetes may not sufficiently express the substantial morbidity and mortality associated with the disease. The chances are that even diabetic patients at their very early stage and individuals potentially at risk, especially by not going for routine check up might take the disease for granted. Routine fasting/random blood sugar (glycemic) and glucosuric (urinalysis) remain important panacea for early detection of diabetes and its management. Most adverse diabetes outcomes are as a result of vascular complications, both of a macrovascular level (coronary artery disease, cerebrovascular disease, or peripheral vascular disease) and a microvascular level; retinopathy and nephropathy.[7]

1.2: STATEMENT OF THE PROBLEM

Diabetes mellitus is a non-communicable disease with a rising prevalence worldwide. Although there is a paucity of data on the prevalence of diabetes in Nigeria and other African countries, available data suggest that diabetes is emerging as a major health problem in Africa, including Nigeria.[8] It is predicted that prevalence of DM in adults will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64[5]. Most of the increase in prevalence is projected to be in the developing countries like Nigeria. The National standardized rate is 2.2% in Nigeria, the crude prevalence rate is 7.4% in those aged 45 years and above who live in urban areas. The increase in incidence follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. The global incidence of type 2 diabetes mellitus (DM) among adultsis high and its economic burden is increasing. Also prevalence rates and risk factors for type 2 diabetes in Nigeria are not well documented and epidemiological evidence suggests that without effective prevention and control programmes, the burden of diabetes is likely to continue to increase globally. There is therefore need to assess the prevalence rates of type 2 diabetes and also determine its potential risk factors in University of Nigeria Nsukka.

1.3: SIGNIFICANCE OF THE STUDY

As it is recognized that the onset of the diabetes and its complications predate the symptoms, it is expedient that screening procedures are undertaken to diagnose the

disease in the individual as early as possible to minimize the risk of complications. Diabetes mellitus is a chronic disease necessitating life-long therapy, usually with drugs. This creates a life-long financial burden on the family, especially in low socio-economic communities in West Africa, where the majority of the population still lives on less than one dollar a day. This affects the wellbeing of the entire family, hence the need for early detection, prompt and adequate management of the disease and avoidance of its complications. Interventions targeting the main risk factors could have a significant impact on reducing the burden of disease worldwide.

1.4: GENERAL OVERVIEW OF DIABETES

Diabetes was one of the first diseases described,[9] with an Egyptian manuscript from 1500 BCE mentioning “too great emptying of the urine”.[10] The first described cases are believed to be of type 1 diabetes.[10] Indian physicians around the same time identified the disease and classified it as *madhumeha* or "honey urine", noting the urine would attract ants.[10] The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Appollonius of Memphis. The disease was rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career. Type 1 and type 2 diabetes where identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 AD with type 1 associated with youth and type 2 with being overweight.[10]

The term "mellitus" or "from honey" was added by the Britain John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination.[10] While many measures where tried, effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Best developed insulin in 1921 and 1922.[10] This was followed by the development of the long acting insulin NPH in the 1940s.[10]

Although they have a common name, diabetes mellitus and diabetes insipidus are two entirely separate conditions with unrelated mechanisms. Both cause large amounts of urine to be produced (polyuria), and the term "diabetes" is derived from the Greek name

for this symptom. However, diabetes insipidus is either a problem with the production of antidiuretic hormone (cranial diabetes insipidus) or kidney's response to antidiuretic hormone (nephrogenic diabetes insipidus), whereas diabetes mellitus causes polyuria via a process called osmotic diuresis, due to the high blood sugar leaking into the urine and taking excess water along with it.[10]

1.4.1: DIABETES INSIPIDUS

The incidence of diabetes insipidus in the general population is 3 in 100,000. Diabetes insipidus (DI) is a condition characterized by excessive thirst and excretion of large amounts of severely diluted urine, with reduction of fluid intake having no effect on the concentration of the urine. There are several different types of DI, each with a different cause. The most common type in humans is central DI, caused by a deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH). The second common type of DI is nephrogenic diabetes insipidus, which is caused by an insensitivity of the kidneys to ADH. It can also be an iatrogenic artifact of drug use.[11]

1.4.1.1: Signs and symptoms of Diabetes Insipidus

Excessive urination and extreme thirst (especially for cold water and sometimes ice or ice water) are typical for DI. Its symptoms are quite similar to those of untreated diabetes mellitus, with the distinction that the urine does not contain glucose and there is no hyperglycemia (elevated blood glucose). Blurred vision is a rarity. Signs of dehydration may also appear in some individuals, since the body cannot conserve much (if any) of the water it takes in. The extreme urination continues throughout the day and the night. In children, DI can interfere with appetite, eating, weight gain, and growth, as well. They may present with fever, vomiting, or diarrhea. Adults with untreated DI may remain healthy for decades as long as enough water is consumed to offset the urinary losses. However, there is a continuous risk of dehydration and loss of potassium.[11]

1.4.1.2: Diagnosis of Diabetes Insipidus

To distinguish DI from other causes of excess urination, blood glucose levels, bicarbonate levels, and calcium levels need to be tested. Measurement of blood

electrolytes can reveal a high sodium level (hypernatremia as dehydration develops). Urinalysis demonstrates a dilute urine with a low specific gravity. Urine osmolarity and electrolyte levels are typically low.[11]

A fluid deprivation test helps determine whether DI is caused by:[11]

- excessive intake of fluid (primary polydipsia)
- a defect in ADH production
- a defect in the kidneys' response to ADH

This test measures changes in body weight, urine output, and urine composition when fluids are withheld and as dehydration occurs. The body's normal response to dehydration is to concentrate urine and conserve water, so urine becomes more concentrated and urination becomes less frequent. Those with DI continue to urinate large amounts of dilute urine in spite of not drinking any fluids. In primary polydipsia, the urine osmolality should increase and stabilize at above 280 Osm/kg with fluid restriction, while a stabilization at a lower level indicates diabetes insipidus.[11] Stabilization in this test means, more specifically, when the hourly increase in osmolality is less than 30 Osm/kg per hour for at least 3 hours.[11] Sometimes measuring blood levels of ADH during this test is also necessary, but is more time consuming to perform.[11]

To distinguish between the main forms, desmopressin stimulation is also used; desmopressin can be taken by injection, a nasal spray, or a tablet. While taking desmopressin, a patient should drink fluids or water only when thirsty and not at other times, as this can lead to sudden fluid accumulation in the central nervous system. If desmopressin reduces urine output and increases osmolarity, the pituitary production of ADH is deficient, and the kidney responds normally. If the DI is due to renal pathology, desmopressin does not change either urine output or osmolarity. If central DI is suspected, testing of other hormones of the pituitary, as well as magnetic resonance imaging, is necessary to discover if a disease process (such as a prolactinoma, or histiocytosis, syphilis, tuberculosis or other tumor or granuloma) is affecting pituitary function. Most people with this form have either experienced past head trauma or have stopped ADH production for an unknown reason. Habit drinking (in its severest form

termed psychogenic polydipsia) is the most common imitator of diabetes insipidus at all ages. While many adult cases in the medical literature are associated with mental disorders, most patients with habit polydipsia have no other detectable disease. The distinction is made during the water deprivation test, as some degree of urinary concentration above isosmolar is usually obtained before the patient becomes dehydrated.[11]

1.4.1.3: Pathophysiology of Diabetes Insipidus

Electrolyte and volume homeostasis is a complex mechanism that balances the body's requirements for blood pressure and the main electrolytes sodium and potassium. In general, electrolyte regulation precedes volume regulation. When the volume is severely depleted, however, the body will retain water at the expense of deranging electrolyte levels. The regulation of urine production occurs in the hypothalamus, which produces ADH in the supraoptic and paraventricular nuclei. After synthesis, the hormone is transported in neurosecretory granules down the axon of the hypothalamic neuron to the posterior lobe of the pituitary gland, where it is stored for later release. In addition, the hypothalamus regulates the sensation of thirst in the ventromedial nucleus by sensing increases in serum osmolarity and relaying this information to the cortex.[12]

The main effector organ for fluid homeostasis is the kidney. ADH acts by increasing water permeability in the collecting ducts and distal convoluted tubules; specifically, it acts on proteins called aquaporins and more specifically aquaporin 2 in the following cascade; ADH (argenine vasopressin-AVP) produced in the hypothalmus and stored in the posterior pituitary. When released, ADH binds to V2 G-protein coupled receptors within the distal convoluted tubules, increasing cyclic AMP, which couples with protein kinase A, stimulating transcription of the aquaporin 2 channel stored in the cytoplasm of the distal convoluted tubules and collecting ducts into the apical membrane. These transcribed channels allow water into the collecting duct cells. The increase in permeability allows for re-absorption of water into the bloodstream, thus concentrating the urine.[11]

Hereditary forms of diabetes insipidus account for less than 10% of the cases of diabetes insipidus seen in clinical practice.[12]

1.4.1.4: Classification of Diabetes Insipidus

The several forms of DI are:[11]

Neurogenic- Neurogenic diabetes insipidus, more commonly known as central diabetes insipidus, is due to a lack of vasopressin production in the brain.

Nephrogenic- Nephrogenic diabetes insipidus is due to the inability of the kidney to respond normally to vasopressin.

Dipsogenic-Dipsogenic DI is due to a defect or damage to the thirst mechanism, which is located in the hypothalamus.[13]This defect results in an abnormal increase in thirst and fluid intake that suppresses vasopressin secretion and increases urine output. Desmopressin is ineffective, and can lead to fluid overload as the thirst remains.

Gestational- Gestational DI only occurs during pregnancy. During pregnancy, all women produce vasopressinase in the placenta, which breaks down ADH. Gestational DI is thought to occur with excessive vasopressinase production.[14]Most cases of gestational DI can be treated with desmopressin. In rare cases, however, an abnormality in the thirst mechanism causes gestational DI, and desmopressin should not be used. Diabetes insipidus is also associated with some serious diseases of pregnancy, including pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy. These cause DI by activating hepatic vasopressinase. It is important to consider these diseases if a woman presents with diabetes insipidus in pregnancy, because their treatments require delivery of the baby before the disease will improve. Failure to treat these diseases promptly can lead to maternal or perinatal mortality.[14]

1.4.1.5: Treatment of Diabetes Insipidus

Central DI and gestational DI respond to desmopressin. Carbamazepine, an anticonvulsive medication, has also had some success in this type of DI. Also, gestational DI tends to abate on its own four to six weeks following labour, though some women may develop it again in subsequent pregnancies. In dipsogenic DI, desmopressin is not usually an option. Desmopressin will be ineffective in nephrogenic DI. Instead, the

diuretic hydrochlorothiazide (a thiazide diuretic) or indomethacin can improve nephrogenic diabetes insipidus. Thiazide diuretics are sometimes combined with amiloride to prevent hypokalemia. It seems paradoxical to treat an extreme diuresis with a diuretic, but the thiazide diuretics will decrease distal convoluted tubule re-absorption of sodium and water, thereby causing diuresis. This decreases plasma volume, thus lowering GFR and enhancing the absorption of sodium and water in the proximal nephron. Less fluid reaches the distal nephron, so overall fluid conservation is obtained.[15]

Lithium-induced nephrogenic DI may be effectively managed with the administration of amiloride, a potassium-sparing diuretic often used in conjunction with thiazide or loop diuretics. Clinicians have been aware of lithium toxicity for many years, and traditionally have administered thiazide diuretics for lithium-induced polyuria and nephrogenic diabetes insipidus. However, amiloride has recently been shown to be a successful treatment for this condition.[16,17]

1.4.2: DIABETES MELLITUS

The prevalence of diabetes mellitus is rising worldwide in both developed and developing countries.[1] Its worldwide prevalence is about 2%, and the prevalence in Nigeria is 2.2%, which means that about 2.6 million Nigerians are diabetic.[2] It is known that 50% of the affected individuals (about 1.3 million Nigerians) do not even know that they have the disease.[4,5] Globally, as of 2010, an estimated 285 million people had diabetes, with type 2 making up about 90% of the cases.[4] Its incidence is increasing rapidly, and by 2030, this number is estimated to almost double.[18] Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030.[18]The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.[18]

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced.[2] This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Complications of diabetes mellitus have been found to set in long before clinical manifestation of the disease.[4,5] The onset of complications of diabetes mellitus can be reduced if the diagnosis is made early and appropriate treatment is commenced promptly. Diabetes mellitus has a serious impact on those affected and their families, hence the need for early detection and prompt and adequate management. Early detection can be enhanced by screening people for the disease on an incidental basis when consulting for other reasons.

It occurs in two major forms, type 1 and type 2 DM, both differ in etiology, pathology, age of onset and treatment. All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both types 1 and 2 are chronic conditions that usually cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyper-osmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.[18]

1.4.2.1: Classification of Diabetes Mellitus

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes and "other specific types".[2] The "other specific types" are a collection of a few dozen individual causes.[2] The term "diabetes", without qualification, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (*insipidus* means "without taste" in Latin). The term "type 1 diabetes" has replaced several former terms, including

childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and noninsulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes,[6] insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes).[7]

1.4.2.2: Type 1 Diabetes Mellitus

Type 1 DM results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus (IDDM) or "juvenile" diabetes)Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell-mediated autoimmune attack.[19]There is no known preventive measure against type 1 diabetes, which causes approximately 10% of DM cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.[19] There are many different reasons for type 1 diabetes to be accompanied by irregular and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemias, including an impaired counterregulatory response to hypoglycemia, occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's

disease).[19] These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.[20]

1.4.2.3: Type 2 Diabetes Mellitus

Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as noninsulin-dependent diabetes mellitus (NIDDM) or "adult-onset" diabetes). Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[2] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

1.4.2.4: GestationalDiabetes Mellitus

Gestational diabetes is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM. Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In

severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

A 2008 study completed in the U.S. found the number of American women entering pregnancy with pre-existing diabetes is increasing. In fact, the rate of diabetes in expectant mothers has more than doubled in the past six years.[21] This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential for the children of diabetic mothers to become diabetic in the future.

Other forms of diabetes mellitus include:

- Congenital diabetes, which is due to genetic defects of insulin secretion.
- Cystic fibrosis-related diabetes.
- Steroid diabetes induced by high doses of glucocorticoids.
- and several forms of monogenic diabetes.
- Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of pre-diabetes which has been termed "America's largest healthcare epidemic."[21–22]

Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistichormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992)

diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.[23]

Table 1.1: Features of Type 1 and Type 2 Diabetes Mellitus

Characteristics	**Type 1**	**Type 2**
Onset (age)	Usually <30	Usually >40
Type of onset	Abrupt	Gradual
Nutritional status	Often thin	Often obese
Clinical symptoms	Polydipsia, polyuria, polyphagia	Often asymptomatic
Ketosis	Present	Absent
Endogenous insulin	Absent	Variable
Insulin therapy	Required	Sometimes
Oral hypoglycemic	Usually not effective	Often effective
Diet	Mandatory with insulin	Mandatory with or without insulin

1.5: CLINICAL MANAGEMENT OF DIABETES MELLITUS

Diet is the cornerstone of the management of diabetes, regardless of the severity of the symptoms or the type of diabetes. Exercise is also an important component in managing diabetes, particularly in obese individuals with NIDDM who may have a component of insulin resistance as a consequence of obesity. Treatment regimens that have proved effective include a calorie restricted diet in combination with exogenous insulin or oral hypoglycemic drugs. However, since diet, exercise, and oral hypoglycemic drugs, often because of noncompliance by the patient, will not always achieve the clinical objectives of controlling the symptoms of diabetes, insulin remains universally important in therapeutic management. The administration of insulin is required for the treatment of type 1 (IDDM) and in cases of type 2 (NIDDM) that are refractory to management with oral hypoglycemic drugs. Because the spectrum of patients with diabetes extends from the totally asymptomatic individual to one with life-threatening ketoacidosis, *therapeutic managementmust be highly individualized.* An important objective is to maintain a glucose level as close to normal as possible without producing frequent hypoglycemia or overly restricting the patient's lifestyle. Many diabetics aim to achieve an average blood glucose below 150 (hemoglobin A1c<7%). Unstable or ketoacidosis prone diabetics are

difficult to maintain with a single dose of either intermediate- or long-acting insulin; they usually require multiple injections of combinations of short-, intermediate-, and/or long-acting insulin preparations.[24]

Goals of therapy in diabetes mellitus are directed at reducing symptoms of hyperglycemia, delaying the onset and progression of retinopathy, nephropathy, and neuropathy complications, intensive therapy for associated cardiovascular risk factors, and improving quality and quantity of life. Metformin should be included in the therapy for all type 2 DM patients, if tolerated and not contraindicated, as it is the only oral antihyperglycemic medication proven to reduce the risk of total mortality and cardiovascular death, according to the United Kingdom Prospective Diabetes Study. Intensive glycemic control is paramount for reduction of microvascular complications (neuropathy, retinopathy, and nephropathy) as evidenced by the Diabetes Control and Complications Trial in type 1 DM and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 DM. The UKPDS also reported that control of hypertension in patients with diabetes will not only reduce the risk of retinopathy and nephropathy, but also reduce cardiovascular risk. Knowledge of the patient's quantitative and qualitative meal patterns, activity levels, pharmacokinetics of insulin preparations, and pharmacology of oral antihyperglycemic agents are essential to individualize the treatment plan and optimize blood glucose control while minimizing risks for hypoglycemia and other adverse effects of pharmacologic therapies.[24]

Treatment of type 2 DM often necessitates use of multiple therapeutic agents (combination therapy), including oral antihyperglycemics and insulin to obtain glycemic goals.Aggressive management of cardiovascular disease risk factors in type 2 DM is necessary to reduce the risk for adverse cardiovascular events or death. Smoking cessation, use of antiplatelet therapy as a primary prevention strategy, aggressive management of dyslipidemia minimally to goal low density lipoprotein-cholesterol (LDL-C) (<100 mg/dL) and secondarily to raise high-density lipoprotein-cholesterol (HDL-C) to ≥40 mg/dL, and treatment of hypertension (again often requiring multiple drugs) minimally to <130/80 mm Hg are vital.[24]

Prevention strategies for type 1 DM have been unsuccessful. Prevention strategies for type 2 DM are established. Lifestyle changes, dietary restriction of fat, aerobic exercise for 30 minutes 5 times a week, and weight loss, form the backbone of successful prevention. To date, medications have been less effective than lifestyle changes to prevent progression to type 2 DM.

Patient education and ability to demonstrate self-care and adherence to therapeutic lifestyle and pharmacologic interventions are crucial to successful outcomes.

Table 1.2: Antidiabetic Drugs

Augment insulin supply	Enhance insulin action	Delay carbohydrate absorption
Sulfonylureas	Biguanides	α-glucosidase inhibitors
Meglitinides	Thiazolidinediones	
Insulin		

1.6: TYPE 2 DIABETES MELLITUS

Diabetes mellitus type 2 – formerly non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes – is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[25] This is in contrast to diabetes mellitus type 1 in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas.[2] The classic symptoms are excess thirst, frequent urination, and constant hunger. Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease.[26]

Type 2 diabetes is initially managed by increasing exercise and dietary modification. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin there is typically the requirement to routinely check blood sugar levels.Rates of diabetes have increased markedly over the last 50 years in parallel with obesity.[27]

Globally as of 2010 it was estimated that there were 285 million people with type 2 diabetes making up about 90% of diabetes cases.[4]This is equivalent to about 6% of the worlds adult population. Diabetes is common both in the developed and the developing world.[4] Women seem to be at a greater risk as do certain ethnic groups,[4] such as South Asians, Pacific Islanders, Latinos, and Native Americans.[4] This may be due to enhanced sensitivity to a Western lifestyle in certain ethnic groups. Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel with rising obesity rates.[4] Type 2 diabetes is now diagnosed as frequently as type 1 diabetes in teenagers in the United States.[2]

Rates of diabetes in 1985 were estimated at 30 million, increasing to 135 million in 1995 and 217 million in 2005.[4] This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity.[4] The five countries with the greatest number of people with diabetes as of 2000 are India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million.[28] It is recognized as a global epidemic by the World Health Organization.[26]

As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor circulation of limbs leading to amputations. The acute complication of ketoacidosis, a feature of type 1 diabetes, is uncommon. However, nonketotic hyper-osmolar coma may occur.[26]

1.6.1: Signs and symptoms Type 2 Diabetes Mellitus

The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss.[29] Other symptoms that are commonly present at diagnosis include: a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue. Many people however have no symptoms during the first few years and are diagnosed on routine testing. People with type 2 diabetes mellitus may rarely present with nonketotic hyper-osmolar coma (a

condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure).[30]

1.6.2: Complications of Type 2 Diabetes Mellitus

Type 2 diabetes is typically a chronic disease, associated with a ten year shorter life expectancy.[64] This is partly due to a number of complications with which it is associated including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke, a 20 fold increase in lower limb amputations, and increased rates of hospitalizations.[4] In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of non-traumatic blindness and kidney failure.[28] It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia.[26] Other complications include: acanthosisnigricans, sexual dysfunction, and frequent infections.[30]

1.6.3: Causes of Type 2 Diabetes Mellitus

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors.[31,32] While some are under personal control such as diet and obesity others such as increasing age, female gender, and genetics are not.[27] A lack of sleep has been linked to type 2 diabetes.[33]This is believed to act through its effect on metabolism.[34] The nutritional status of a mother during fetal development may also play a role with one proposed mechanism being that of altered DNA methylation.[28]

1.6.3.1: Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes including: obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization.[4] Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.[2] Those who are not obese often have a high waist–hip ratio.[2] Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar sweetened drinks in excess is

associated with an increased risk.[32,35] The type of fats in the diet are also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.[35] Eating lots of white rice appears to also play a role in increasing risk.[34]

1.6.3.2: Genetics

Most cases of diabetes involve many genes with each being a small contributor to an increased probability of becoming a type 2 diabetic.[4] If one identical twin has diabetes the chance of the other developing diabetes within their lifetime is greater than 90% while the rate for non-identical siblings is 25-50%.[2] As of 2011, more than 36 genes have been found that contribute to the risk of type 2 diabetes.[32] All of these genes together still only account for 10% of the total heritable component of the disease. The TCF7L2allele for example increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants. Most of the genes linked to diabetes are involved in beta cell functions.[2]

There are a number of rare cases of diabetes that arise due to an abnormality in a single gene (known as monogenic forms of diabetes or "other specific types of diabetes").[4,30] These include maturity onset diabetes of the young (MODY), Donohue syndrome, and Rabson-Mendenhall syndrome, among others.[4] Maturity onset diabetes of the young constitute 1–5 % of all cases of diabetes in young people.[36]

1.6.3.3: Medical conditions

There are a number of medications and other health problems that can predispose to diabetes.[37] Some of the medications include: glucocorticoids, thiazides, beta blockers, atypical antipsychotics,[38] and statins.[39] Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes.[30] Other health problems that are associated include: acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, and certain cancers such as glucagonomas.[37]Testosterone deficiency is also associated with type 2 diabetes.[40,41]

1.6.4: Pathophysiology of Type 2 Diabetes Mellitus

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance.[2] Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver and fat tissue.[42] In the liver insulin normally suppressed glucose release, however in the setting of insulin resistance the liver inappropriately releases glucose into the blood.[4] The proportion of insulin resistance verses beta cell dysfunction differs among individuals with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion.[2]

Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system.[4] However not all people with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required.[38]

Diabetic emergencies- People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell of acetone, a rapid, deep breathing known as Kussmaul breathing, nausea, vomiting and abdominal pain, and altered states of consciousness. A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration.[43]

Complications-All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease.[44] The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "microvascular" complications—damage to the small blood vessels.[45]Diabetic retinopathy, which affects blood vessel formation in the retina of the

eye, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

1.6.5: Diagnosisof Type 2 Diabetes Mellitus

The World Health Organization definition of diabetes (both type 1 and type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:[46,47]

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)
  or
- with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

A random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms[30,47] or a glycated hemoglobin (HbA_{1c}) of greater than 6.5% is another method of diagnosing diabetes.[4] In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of ≥6.5% HbA_{1c} should be used to diagnose diabetes. This recommendation was adopted by the American Diabetes Association in 2010.[49] Positive tests should be repeated unless the person presents with typical symptoms and blood sugars >11.1 mmol/l (>200 mg/dl).[49]

Threshold for diagnosis of diabetes are based on the relationship between results of glucose tolerance tests, fasting glucose or HbA_{1c} and complications such as retinal

problems.[4] A fasting or random blood sugar is preferred over the glucose tolerance test as they are more convenient for people.[4] HbA_{1c} has the advantages that fasting is not required and results are more stable, but has the disadvantage that the test is more costly than measurement of blood glucose.[50] It is estimated that 20% of people with diabetes in the United States do not realize that they have the disease.[4] Diabetes mellitus type 2 is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[51] This is in contrast to diabetes mellitus type 1 in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas and gestational diabetes mellitus that is a new onset of high blood sugars in associated with pregnancy.[3] Type 1 and type 2 diabetes can typically be distinguished based on the presenting circumstances.[52] If the diagnosis is in doubt antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes.[53,54]

1.6.6: Metabolic disturbances and complications of the diabetic state

There are only two major sources of blood glucose: exogenous, or the ingestion of dietary carbohydrate, and endogenous, which is contributed by hepatic and renalgluconeogenesis and hepatic glycogenolysis. Diabetes mellitus is a metabolic disorder in which carbohydrate metabolism is reduced while that of proteins and lipids is increased. In diabetics, exogenous and endogenous glucoseis not used effectively, and it accumulates in theblood (hyperglycemia). As blood glucose levels increase,the amount of glucose filtered by the glomerulieventually exceeds the re-absorption capacity (Tm, transportmaximum) of the proximal tubule cells, and glucoseappears in the urine (glucosuria). Protein catabolismand the rate of nitrogen excretion are increasedwhen blood insulin falls to low levels; stimulation of hepaticgluconeogenesis converts amino acids to glucose.The catabolism of lipids and fatty acids is also acceleratedin the absence of insulin, leading to the formation of ketone bodies, such as acetoacetic acid, β-hydroxybutyricacid, and acetone. Renal losses of glucose, nitrogenous substances, and ketone bodies promote osmotic diuresis that can result in dehydration, electrolyte abnormalities,and acid–base disturbances.[43]

Diabetic ketoacidosis is the end result of insulin deficiency in uncontrolledtype I diabetes.Type 2 diabetics are less prone to develop ketonebodies or diabetic ketoacidosis

but may develop hyper-osmolar coma, a condition characterized by severe hyper-glycemiaand dehydration. Both diabetic ketoacidosisand hyper-osmolar coma are medical emergenciesthat require prompt insulin administration and intravenousfluids.Diabetes mellitus is associated with many complicationsthat are increased in the setting of poor glycemic control. Diabetes mellitus can cause microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular complications (e.g., atherosclerotic cardiovascular disease), associated with diabetic dyslipidemia (usually elevated triglycerides and low-density lipoprotein cholesterol). Recent clinical trials have demonstrated that the risk of developing chronic complications of diabetes is reduced by achieving good glycemic control. This can be accomplished by a combination of diet, exercise, and rational pharmacological therapy directly targeted to optimize diabetes management.

1.6.7: Prevention of Type 2 Diabetes Mellitus

Onset of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise.[18,54,55] Intensive lifestyle measures may reduce the risk by over half.[28] The benefit of exercise occurs regardless of the person's initial weight or subsequent weight loss.[56] Evidence for the benefit of dietary changes alone however is limited.[57] with some evidence for a diet high in green leafy vegetables[58] and some for limiting the intake of sugary drinks.[32] In those with impaired glucose tolerance, diet and exercise either alone or in combination with metformin or acarbose may decrease the risk of developing diabetes.[28,59] Lifestyle interventions are more effective than metformin.[28]

1.6.8: Management of Type 2 Diabetes Mellitus

Management of type 2 diabetes focuses on lifestyle interventions, lowering other cardiovascular risk factors, and maintaining blood glucose levels in the normal range.[28] Self-monitoring of blood glucose for people with newly diagnosed type 2 diabetes was recommended by the National Health Services in 2008,[57] however the benefit of self monitoring in those not using multi-dose insulin is questionable.[28] Managing other cardiovascular risk factors including: hypertension, high cholesterol, and

microalbuminuria, improves a person's life expectancy.[28] Intensive blood sugar lowering (HbA1C<6%) as opposed to standard blood sugar lowering (HbA1C of 7-7.9%) does not appear to change mortality.[90,91] The goal of treatment is typically an HbA1C of less than 7% or a fasting glucose of less than 6.7 mmol/L (120 mg/dL) however these goals may be changed after professional clinical consultation, taking into account particular risks of hypoglycemia and life expectancy.[30] It is recommended that all people with type 2 diabetes get regular ophthalmology examination.[2]

1.6.8.1: Lifestyle Modifications

A proper diet and exercise are the foundations of diabetic care[30] with a greater amount of exercise yielding better results.[60]Aerobic exercise leads to a decrease in HbA1C and improved insulin sensitivity.[60]Resistance training is also useful and the combination of both types of exercise may be most effective.[61] A diabetic diet that promotes weight loss is important.[61] While the best diet type to achieve this is controversial[61] a low glycemic index diet has been found to improve blood sugar control.[62] Culturally appropriate education may help people with Type 2 diabetes control their blood sugar levels, for up to six months at least.[62] If changes in lifestyle, in those with mild diabetes, has not resulted in improved blood sugars within six weeks medications should then be considered.[30]

1.6.9: Medications for Type 2 Diabetes Mellitus

Although insulin has the disadvantage of having to be injected, it is without question the most uniformly effective treatment of diabetes mellitus. Some milder forms of diabetes mellitus that do not respond to diet management or weight loss and exercise can be treated with oral hypoglycemic agents. The success of oral hypoglycemic drug therapy is usually based on a restoration of normal blood glucose levels and the absence of glycosuria. Traditionally, the term *oral hypoglycemic* was used interchangeably with sulfonylureas, but more recently the development of several new drugs has broadened this designation to include all oral medications for diabetes. Because these drugs do not have to be injected, oral agents enhance compliance in type II diabetics. These classes of drugs are not generally used in type I diabetes.[28]

1.6.9.1 Sulfonylureas

Sulfonylureas are the most widely prescribed drugs in the treatment of type II diabetes mellitus. The initial sulfonylureas were introduced nearly 50 years ago and were derivatives of the antibacterial sulfonamides. Although their structural similarities to the sulfonamide antibacterial agents are readily apparent, the sulfonylureas possess no antibacterial activity.

Mechanism of Action-The primary mechanism of action of the sulfonylureas is *direct stimulation of insulin release from the pancreatic* β*-cells.* In the presence of viable pancreatic β-cells, sulfonylureas enhance the release of endogenous insulin, thereby reducing blood glucose levels.At higher doses, these drugs also decrease hepatic glucose production, and the second-generation sulfonylureas may possess additional extrapancreatic effects that increase insulin sensitivity, though the clinical significance of these pharmacological effects is unclear.[63]

The sulfonylureas are *ineffective* for the management of type I and severe type II diabetes mellitus, since the number of viable β-cells in these forms of diabetes is small. Severely obese diabetics often respond poorly to the sulfonylureas, possibly because of the insulin resistance that often accompanies obesity.

Absorption, Metabolism, and Excretion- Sulfonylureas are readily absorbed from the gastrointestinal tract following oral administration but undergo varying degrees and rates of metabolism in the liver and/or kidney; some metabolites possess intrinsic hypoglycemic activity. Thus, the biological half-lives of the sulfonylureas vary greatly, and a comparison of the drug half-life with the observed duration of action does not always show a good correlation. Sulfonylureas and their metabolites are excreted either renally or in the feces.[28]

Clinical Uses- Sulfonylureas are generally effective in individuals with mild to moderate type II diabetes. The chance for successful glycemic control with sulfonylureas is poor in diabetic patients requiring more than 40 units of insulin per day. When beginning therapy

with one of these drugs, a low to intermediate dose is given initially and then gradually increased until the dosage results in normoglycemia. Once the maximum recommended dosage for a particular sulfonylurea is reached, further increasing the dose will not improve glycemic control.

Adverse Effects and Drug Interactions-The most common adverse effect associated with sulfonylurea administration is hypoglycemia, which may be provoked by inadequate calorie intake (e.g., skipping a meal), or increased caloric needs (e.g., increased physical activity). Collectively, sulfonylureas also tend to cause weight gain, which is undesirable in individuals who already are obese. Some of this weight can be due to fluid retention and edema. Less common adverse reactions include muscular weakness, ataxia, dizziness, mental confusion, skin rash, photosensitivity, blood dyscrasias, and cholestatic jaundice. Occasionally, persons who display drug sensitivities to sulfa-containing antibiotics show across-reactivity to the sulfonylureas. In this situation, a nonsulfonylurea insulin secretagogue can be used (if desired), such as repaglinide or nateglinide. Sulfonylureas are not used in gestational diabetes, which is generally managed by a combination of intensive diet control and insulin. Since diabetic patients with renal or hepatic disease are particularly vulnerable to hypoglycemia, the sulfonylurea compounds should be avoided in these individuals.[63]

A decrease in alcohol tolerance also has been observed in some patients taking sulfonylurea compounds. Since sulfonylureas are highly bound to plasma proteins and are extensively metabolized by microsomal enzymes, co-administration of drugs capable of displacing them from their protein binding sites or inhibiting their metabolism (e.g., sulfonamide antibacterials, propranolol, salicylates, phenylbutazone, chloramphenicol, probenecid, and alcohol) also may potentiate hypoglycemia.[28,64]

First-Generation Sulfonylureas- The first-generation sulfonylureas are not frequently used in the modern management of diabetes mellitus because of their relatively low specificity of action, delay in time of onset, occasional long duration of action, and a variety of side effects. They also tend to have more adverse drug interactions than the

second-generation sulfonylureas. They are occasionally used in patients who have achieved previous adequate control with these agents.

Acetohexamide (*Dymelor*) is the only sulfonylurea with uricosuric activity, an action that may be of benefit in diabetic patients who also have gout. Chlorpropamide (*Diabinese*) has a relatively slow onset of action, with its maximal hypoglycemic potential often not reached for 1 or 2 weeks. Similarly, several weeks may be required to eliminate the drug after discontinuation of therapy. This drug can cause flushing, particularly when taken with alcohol, and can also cause hyponatremia. This effect has been employed to treat some patients who have partial central diabetes insipidus, an unrelated condition due to a pituitary ADH deficiency. Tolazamide (*Tolinase*) is an orally effective hypoglycemic drug that causes less water retention than do the other compounds in this class. Tolbutamide (*Orinase*) is a relatively short-acting compound that may be useful in patients who are prone to hypoglycemia.[28,64]

Second-Generation Sulfonylureas- The second-generation sulfonylureas display a higher specificity and affinity for the sulfonylurea receptor and more predictable pharmacokinetics in terms of time of onset and duration of action, and they have fewer side effects. Second-generation sulfonylureas may also exert mild diuretic effects on the kidney and are highly protein bound, primarily through nonionic binding (in contrast to the ionic binding observed with the first-generation compounds). Glyburide (*DiaBeta, Micronase,Glynase*), also known as glibenclamide, is approximately 150 times as potent as tolbutamide on a molar basis and twice as potent as glipizide (discussed later). Glyburide is completely metabolized in the liver to two weakly active metabolites before excretion in the urine. Its average duration of action is 24 hours. Glipizide (*Glucotrol*) is similar to glyburide, but it is metabolized by the liver to two inactive metabolites; these metabolites and glipizide are renally excreted. Glimepiride (*Amaryl*) is metabolized to at least one active metabolite. It is quickly absorbed from the gastrointestinal tract within an hour of oral administration and excreted in the urine and feces. Its half-life varies from 5 to 9 hours depending on the frequency of multiple dosing.

1.6.9.2: Meglitinides

Though structurally unrelated to sulfonylureas, the meglitinideclass of hypoglycemic drugs bind to the same KATP channel as do the sulfonylureas, but it is unclear whether they bind to the same SUR1 subunit within the KATP complex. As a class, the meglitinides are incapable of stimulating insulin secretion in nutrientstarved β-cells, but in the presence of glucose, they demonstrate hypoglycemic effects by augmenting the release of insulin. Consequently, meglitinides seem relatively unlikely to cause fasting hypoglycemia.[63]

Repaglinide (*Prandin*), a member of the meglitinide class, is approved for monotherapy or in combination with metformin. Repaglinide is taken before each meal, three times a day, and is rapidly absorbed; it is metabolized by the liver and has a half life of an hour. Insulin levels transiently rise postprandially after repaglinide administration but generally return to baseline by the next meal. Although repaglinide does not appear to offer any advantage over the sulfonylureas, it may be helpful in patients with a known allergy to sulfa drugs.

Hypoglycemia is the most common side effect. Nateglinide (*Starlix*), a newer drug in the meglitinide class, is a phenylalanine derivative that also works by binding to a specific site on the K–ATP–sensitive channel on the surface of B-cells. Nateglinide binds with a higher affinity than doesrepaglinide and has a faster onset of action and a shorter duration of action. Like repaglinide, it is approved for both monotherapy and in combination with metformin. Nateglinide is taken three times a day before meals and achieves peak plasma levels within an hour. Nateglinide administration results in plasma insulin levels that peak within 2 hours; they return to baseline by 4 hours. Nateglinide is metabolized by the liver and excreted by the kidney. The main side effect of nateglinide is hypoglycemia, though its effects on fasting insulin levels is not substantially reduced.

1.6.9.3: Biguanides

Biguanides are a group of oral hypoglycemic agents that are chemically and pharmacologically distinct from the sulfonylureas. One biguanide, phenformin, was

briefly used in the United States more than 30 years ago but was withdrawn from the market because it produced severe lactic acidosis in some patients. Metformin (*Glucophage*) was used in Europe for many years before it was approved for use in the United States in 1995. Metformin is the only approved biguanide for the treatment of patients with NIDDM that are refractory to dietary management alone. Metformin does not affect insulin secretion but requires the presence of insulin to be effective. The exact mechanism of metformin's action is not clear, but it does decrease hepatic glucose production and increase peripheral glucose uptake. When used as monotherapy, metformin rarely causes hypoglycemia. Metformin works best in patients with significant hyperglycemia and is often considered first-line therapy in the treatment of mild to moderate type II overweight diabetics who demonstrate insulin resistance. The United Kingdom Prospective Diabetes Study demonstrated a marked reduction in cardiovascular comorbidities and diabetic complications in metform in treated individuals.[24] Metformin has also been used to treat hirsutism in individuals with polycystic ovarian syndrome and may enhance fertility in these women, perhaps by decreasing androgen levels and enhancing insulin sensitivity.[24]

Adverse gastrointestinal symptoms (nausea, vomiting, anorexia, metallic taste, abdominal discomfort, and diarrhea) occur in up to 20% of individuals taking metformin; this can be minimized by starting at a low dose and slowly titrating the dose upward *with food.* Like phenformin, metformin can cause lactic acidosis, but its occurrence is rare except when renal failure, hypoxemia, or severe congestive heart failure is present or when co-administered with alcohol. Metformin is also contraindicated in persons with hepatic dysfunction, but it appears to be safe for use in the hepatic steatosis that often occurs with fatty infiltration of the liver in poorly controlled type II diabetics. Two relatively new formulations of metformin are available. *Glucovance*is a combination of metformin and glyburide that may be helpful for diabetics who require both a sulfonylurea and metformin, and *GlucophageXR*is an extended-release product of metformin that may be better tolerated in some patients who are prone to gastrointestinal side effects. Metformin is usually given two to three times a day at mealtimes.[63]

1.6.9.4: Thiazolidinediones

Thiazolidinediones (sometimes termed glitazones) are a novel class of drugs that were initially identified for their insulin-sensitizing properties. They all act to decrease insulin resistance and enhance insulin action in target tissues. Thiazolidinediones activate the nuclear peroxisome proliferator–activated receptor (PPAR) γ, a nuclear orphan receptor that is predominantly expressed in adipose tissue and to a lesser extent in muscle, liver, and other tissues. The endogenous ligand for the PPAR-γ receptor is postulated to be prostaglandin J2, and it appears to work by heterodimerizing with other nuclear receptors to modulate the expression of insulin-sensitive genes. Thiazolidinediones are readily absorbed from the gastrointestinal tract following oral administration and are rapidly metabolized by the liver. Plasma elimination half-life is 2 to 3 hours for rosiglitazone (*Avandia*) and slightly longer for pioglitazone (*Actos*). About two-thirds of conjugated metabolites appear in the urine and the remainder in the feces. The biological effect of these drugs takes several weeks to develop, although patients may see some benefit within a few days to a week. Generally, however, the insulin-sensitizing action of the thiazolidinediones takes a while to develop. For that reason, upward adjustments in dosage are made gradually to avoid hypoglycemia.[65,66]

The patient who would benefit the most from a thiazolidinedione is a type II diabetic with a substantial amount of insulin resistance (e.g., one who does not respond to other oral therapies or who requires excessive amounts of insulin [>100 units/day]). Improvements in diabetic control are variable, ranging from a 1% reduction in hemoglobin A1c when used as monotherapy to greater reductions (>2% reduction in hemoglobin A1c) when used in combinations with other agents, such as sulfonylureas or metformin. Rosiglitazone is approved for use as monotherapy and in conjunction with metformin, though it is sometimes combined with a sulfonylurea or insulin. It is usually taken once or twice a day with or without food. Rosiglitazone may cause a modest increase in lowdensity lipoprotein and triglyceride concentrations, but it is unclear whether this effect has any clinical significance or persists in the long term. Pioglitazone is approved for use as monotherapy and in conjunction with metformin, sulfonylureas, and insulin. It is taken once a day with or without food. Though pioglitazone may also cause a small

increase in low-density lipoprotein concentrations, there is usually a modest decrease in triglyceride levels, but it unclear whether this has any clinical significance or persists in the long term. The original prototype of this class of drugs, troglitazone (*Rezulin*), was taken off the U.S. market in 2000 because of increasing concerns about idiosyncratic hepatic toxicity that resulted in several deaths worldwide. Consequently, frequent monitoring of liver transaminases is recommended for rosiglitazone and pioglitazone, and these drugs should be stopped if transaminases rise to more than two to three times the upper limit of normal. To date, rosiglitazone and pioglitazone seem to be associated with far fewer incidents of hepatic toxicity.[66]

Thiazolidinediones commonly cause edema that can be quite severe, sometimes requiring cessation of the drug, but mild cases of lower extremity edema can be treated with a low dose of a diuretic. There is often a modest amount of weight gain that is independent of water-retaining effects. In laboratory animals, thiazolidinediones at high doses are associated with ultrastructuralhistopathological changes in cardiac tissue; therefore, thiazolidinedione use is contraindicated in patients with significant heart failure. Thiazolidinediones can also cause mild anemia. Safety in pregnancy is not established.[66]

Hypoglycemia is rare with thiazolidinedione monotherapy; however, these drugs may potentiate the hypoglycemic effects of concurrent sulfonylurea or insulin therapy. If a thiazolidinedione is to be added to a diabetic's regimen, the sulfonylurea or insulin dosage should be decreased to compensate for any enhanced insulin sensitivity. Occasionally a small portion of insulin-treated type II diabetics may be capable of coming off their insulin altogether, depending on their responsiveness to thiazolidinedione action.[67,68]

1.6.9.5: *α-Glucosidase Inhibitors*

The α-glucosidase inhibitors primarily act to decreasepostprandial hyperglycemia by *slowing the rate* at whichcarbohydrates are absorbed from the gastrointestinaltract. They act by competitively inhibiting α-glucosidases,a group of enzymes in the intestinal brush borderepithelial cells that includes glycoamylase, sucrase, maltase,anddextranase. The

prolongation of the intestinalabsorption of carbohydrates results in a blunted insulinresponse, keeping postprandial hyperglycemia undercontrol. To be effective, α-glucosidase inhibitors must be taken before or with meals. Theoretically, the α-glucosidase inhibitors are most beneficial in patientswith mild to moderate diabetes whose diet is more than50% carbohydrates. α-Glucosidase inhibitors are not approved for used in type I diabetes.[29,69]

Acarbose (*Precose*) is an oligosaccharide derivative that has a higher affinity for the α-glucosidase enzymes than do other dietary oligosaccharides. Systemic absorption of acarbose is very low (~2%), with most being broken down in the intestine to several metabolites. About half of the orally administered acarbose is excreted unchanged in the feces, while the remainder, some of which is systemically absorbed, is renally excreted. Acarbose may be associated with hepatotoxicity in rare instances. Miglitol (*Glyset*) is another α-glucosidase inhibitor, but in contrast to acarbose, miglitol is systemically absorbed prior to its activity in the small intestine. It also appears to inhibit the enzymes sucrase and maltase to a greater extent than does acarbose. It does not undergo metabolism and is renally excreted unchanged. Gastrointestinal disturbances (loose stools, flatulence, and abdominal cramping) are the most frequently observed side effects of the α -glucosidase inhibitors. These effects can be minimized by starting patients on a low dose and then slowly advancing the dose as tolerance develops; curtailment of carbohydrate consumption also can alleviate these effects. Patients should be counseled that these side effects will occur and that tolerance should develop; otherwise, compliance will be low and about one-third of patients will stop their medication.[69]

Unlike the sulfonylureas, insulin, and the thiazolidinediones, α-glucosidase inhibitors do not cause weight gain. Insulin levels do not change in the presence of α-glucosidase inhibitors, so fasting hypoglycemia does not occur when α-glucosidase inhibitors are used as monotherapy. Although the α-glucosidase inhibitors may be used as monotherapy, they are usually used in combination with metformin, sulfonylureas, or insulin. Under the best circumstances, α -glucosidaseinhibitorscan be expected to promote a 0.5 to 1% reduction in a patient's hemoglobin A1c. Leaving aside their gastrointestinal side effects, α-glucosidase inhibitors appear to be relatively safe.[69]

Table 1.3: Pharmacokinetic Properties of Oral Hypoglycemic Drugs

Drug	Half-life (hr)	Duration of action (hr)	Activity of metabolite
Sulfonylureas			
First generation			
Acetohexamide	0.8-2.4	12-18	+
Chlorpropamide	24-48	12-18	+
Tolazamide	4-7	60	+
Tolbutamide	3-28	12-24	-
Second generation			
Glyburide	2-4	16-24	±
Glipizide	1-5	12-24(XL >24)	-
Glimeperide	5-9	>24	+
Meglitinides			
Repaglinide	1	4-6	-
Nateglinide	1	2-4	-
Biguanides			
Metformin	4-8	18-24	-
α-Glucosidase inhibitors			
Acarbose	2	4-6	±
Miglitol	2	4-6	-
Thiazolidinediones			
Pioglitazone	26-30	Days	-
Rosiglitazone	4	Days	-

1.6.9.6: Other Anti-diabetics

Peptide analogs

Injectable Incretinmimetics

Incretins are insulin secretagogues. The two main candidate molecules that fulfill criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).[70]

Injectable Glucagon-like peptide analogs and agonists

Glucagon-like peptide (GLP) agonists bind to a membrane GLP receptor.[70] As a consequence, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half-life of only a few minutes, thus an analogue of GLP would not be practical. Exenatide (also Exendin-4, marketed as Byetta) is the first GLP-1 agonist approved for the treatment of type 2 diabetes. Exenatide is not an analogue of GLP but rather a GLP agonist.[72,73]Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life.[71] Typical reductions in hemoglobin A1c values are 0.5–1.0%. Liraglutide, a once-daily human analogue (97% homology), has been developed by Novo Nordisk under the brand name Victoza.

These agents may also cause a decrease in gastric motility, responsible for the common side-effect of nausea, and is probably the mechanism by which weight loss occurs.

Gastric inhibitory peptide analogs

None are FDA approved and they are:

1 Dipeptidyl Peptidase-4 Inhibitors

GLP-1 analogs resulted in weight loss and had more gastrointestinal side-effects, while in general DPP-4 inhibitors were weight-neutral and increased risk for infection and headache, but both classes appear to present an alternative to other antidiabetic drugs. However, weight gain and/or hypoglycaemia have been observed when DPP-4 inhibitors were used with sulfonylureas; effect on long-term health and morbidity rates are still

unknown.[74]Dipeptidyl peptidase-4 (DPP-4) inhibitors increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4.

Examples are:

- vildagliptin (Galvus)
- sitagliptin (Januvia)
- saxagliptin (Onglyza)
- linagliptin (Tradjenta)
- allogliptin
- septagliptin

DPP-4 inhibitors lowered hemoglobin A1c values by 0.74%, comparable to other antidiabetic drugs.[75]

2. Injectable Amylin analogues

Amylin agonist analogues slow gastric emptying and suppress glucagon. They have all the incretins actions except stimulation of insulin secretion. As of 2007, pramlintide is the only clinically available amylin analogue. Like insulin, it is administered by subcutaneous injection. The most frequent and severe adverse effect of pramlintide is nausea, which occurs mostly at the beginning of treatment and gradually reduces. Typical reductions in hemoglobin A1c values are 0.5–1.0%.[76]

1.6.9.7: Alternative medicine

A number of medicinal plants have been studied for the treatment of diabetes, however there is insufficient evidence to determine their effectiveness.[77] Cinnamon has blood sugar-lowering properties, however whether or not it is useful for treating diabetes is unknown.[78] While chromium supplements have no beneficial effect on healthy people, there might be an improvement in glucose metabolism in those with diabetics, although the evidence for this effect remains weak.[79]Vanadyl sulfate, a salt of vanadium, is still in preliminary studies.[80] There is tentative research that thiamine may prevent some diabetic complications however more research is needed.[81]

1.6.9.8: Surgery

Weight loss surgery in those who are obese appears to be an effective measure to treat diabetes.[82]Many are able to maintain normal blood sugar levels with little or no medications following surgery[83] and long term mortality is decreased.[84] There however is some short term mortality risk of less than 1% from the surgery.[85]Thebody mass index cutoffs for when surgery is appropriate are not yet clear.[84]

Patient education, understanding, and participation is vital, since the complications of diabetes are far less common and less severe in people who have well-managed blood sugar levels.[86,87] The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher.[88] Attention is also paid to other health problems that may accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.[88]

There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.[89]

1.6.9.9: Exercise

Physical exercise is any bodily activity that enhances or maintains physical fitness and overall health and wellness. It is performed for various reasons including strengthening muscles and the cardiovascular system, honing athletic skills, weight loss or maintenance, as well as for the purpose of enjoyment. Frequent and regular physical exercise boosts the immune system, and helps prevent the "diseases of affluence" such as heart disease, cardiovascular disease, Type 2 diabetes and obesity. It also improves mental health, helps prevent depression, helps to promote or maintain positive self esteem, and can even augment an individual's sex appeal or body image, which is also found to be linked with higher levels of self esteem. Childhood obesity is a growing global concern and physical exercise may help decrease some of the effects of childhood and adult obesity. Health care providers often call exercise the "miracle" or "wonder" drug—alluding to the wide variety of proven benefits that it provides.[82] Physical exercise is important for

maintaining physical fitness and can contribute positively to maintaining a healthy weight, building and maintaining healthy bone density, muscle strength, and joint mobility, promoting physiological well-being, reducing surgical risks, and strengthening the immune system.

Exercise reduces levels of cortisol, which causes many health problems, both physical and mental. Frequent and regular aerobic exercise has been shown to help prevent or treat serious and life-threatening chronic conditions such as high blood pressure, obesity, heart disease, Type 2 diabetes, insomnia, and depression. Endurance exercise before meals lowers blood glucose more than the same exercise after meals. According to the World Health Organization, lack of physical activity contributes to approximately 17% of heart disease and diabetes, 12% of falls in the elderly, and 10% of breast cancer and colon cancer.

1.6.9.10 Diabetic diet

The *Pritikin Diet* consists of fruit, vegetables, whole grains, and so on, and is high in carbohydrates and roughage. The diet is accompanied by exercise.

G.I. Diet – lowering the glycemic index of one's diet can improve the control of diabetes.This includes avoidance of such foods as potatoes cooked in certain ways, and white bread, and instead favoring multi-grain and sourdough breads, legumes and whole grains—foods that are converted more slowly to glucose in the bloodstream.

Low Carb Diet – It has been suggested that the gradual removal of carbohydrates from the diet and replacement with fatty foods such as nuts, seeds, meats, fish, oils, eggs, avocados, olives, and vegetables may help reverse diabetes. Fats would become the primary calorie source for the body, and complications due to insulin resistance would be minimized.

High fiber diet – It has been shown that a high fiber diet works better than the diet recommended by the American Diabetes Association in controlling diabetes, and may control blood sugar levels with the same efficacy as oral diabetes drugs.

Paleolithic diet – The Paleolithic diet has been shown to improve glucose tolerance in humans with diabetes type 2, humans with ischemic heart disease and glucose intolerance, and in healthy pigs. These are a limited number of studies in a limited

number of subjects, but the knowledge about the benefits of the Paleolithic diet in diabetes is emerging.

1.7 RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

Type 2 diabetes is sometimes described as a 'lifestyle disease' because it is more common in people who do insufficient physical activity and are overweight or obese. It is strongly associated with high blood pressure, high cholesterol and an 'apple' body shape, where excess weight is carried around the waist. Sedentary lifestyles and lack of physical exercise pose more threat to diabetes mellitus pathology.

People at risk need to have a laboratory blood glucose test (not using a portable blood glucose meter) performed by their doctor to check if they have diabetes. This test is preferably done after fasting. It is important not to wait for symptoms to develop as these may not appear until the blood glucose is quite high.

The following are some risk factors of type 2 diabetes:

1.7.1: Hypertension

Uncontrolled hypertension is associated with serious end-organ damage including heart disease, stroke, blindness, and renal disease.[90,91]Cardiovascular diseases (CVDs) are important causes of worldwide preventable morbidity and mortality.[92,93] According to WHO (2004), CVD is responsible for between 50% and 80% of deaths in people with diabetes. CVDs have become a leading cause of mortality and morbidity in developing countries and rates are expected to rise further over the next few decades.[94,95] Relative to white subjects, Afro-Caribbean and people of African descent have high incidence of stroke and end stage renal failure whereas coronary heart disease is less common.[96-98] Once considered a problem only in high-income countries, the prevalence of CVD risk factors is dramatically increasing in low- and middle-income African countries, particularly in urban areas.[98,99] Hypertension is the most common cardiovascular disease which has been the cause of increasing incidence of deaths.

Hypertension also known as high blood pressure is a medical condition in which the blood circulates through the arteries with too much force.[51] It is defined as a disturbance

in hemodynamic function in which there is persistent abnormal elevation of systemic blood pressure of systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg.[99]The 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Prevention reported that as many as 58 million Americans suffer from elevated blood pressure making it one of the most prevalent chronic diseases seen in medical practice.[100] Prevalence rate increases with age and it is higher in blacks (30%) than in whites (25%).[100]Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system. Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in people for whom lifestyle changes prove ineffective or insufficient.

Hypertension is the commonest non-communicable disease and the leading cause of cardiovascular disease in the world.[92,93] It is an important public health challenge in both economically developing and developed countries. Many people with hypertension are unaware of their condition, and among those with hypertension, treatment is infrequent and inadequate. The prevalence of hypertension varies around the world with the lowest prevalence in rural India (3.4% in men and 6.8% in women) and the highest prevalence in Poland (68.9% in men and 72.5% in women). The global prevalence of hypertension has been increasing. In 2000, 972 million people had hypertension with a prevalence rate of 26.4%. These are projected to increase to 1.54 billion affected individuals and a prevalence rate of 29.2% in 2025.[93] Incidence rates of hypertension range from 3% to 18% depending on the age, gender, ethnicity, and body size of the population studied.[94]Studies in Tanzania have reported high rates of hypertension in both urban and

rural areas, particularly among the obese and elderly.[98] In Ghana, earlier studies revealed hypertension prevalence to be 4.5% among rural dwellers and 8% to 13% in the urban dwellers.[99]

A recent community based study of rural and semiurban population in Enugu, Nigeria put the prevalence of hypertension in Nigeria at 32.8%.[95] These serious complications of hypertension can be prevented by adequate blood pressure control.[98,99] Prevention programmes start with screening to identify the population at risk and treatment.

1.7.2: Obesity

Rates of diabetes have increased markedly over the last 50 years in parallel with obesity.[34]Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel with rising obesity rates.[4]

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) if their BMI is between 25 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2. Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness. Evidence to support the view that some obese people eat little yet gain weight due to a slow metabolism is limited; on average obese people have a greater energy expenditure than their thin counterparts due to the energy required to maintain an increased body mass.

Table 1.4: Body mass index (BMI) Classification according to the recommendations of the WHO expert committee for the classification of overweight.[101]

BMI (Kg/m^2)	Classification
<18.5	Underweight
18.5 – 24.9	Normal weight
25.0 – 29.9	Overweight
30.0 – 34.9	Class I obesity
35.0 – 39.9	Class II obesity
≥40.0	Class III obesity

Obesity is by far the strongest modifiable risk factor for type 2 diabetes. [100,102]It is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. There are reports in the literature that 95% of male and almost all of the female diabetics are overweight by the WHO standard at the onset of the disease.[103] They gain more weight during pregnancy, and this weight is not entirely shed afterwards. The increased body fat and weight, together with stress, increase their risk of type 2 diabetes mellitus. Overweight and obesity are leading risk factors for a number of chronic diseases, including CVD, diabetes mellitus, and cancer.[104] Obesity is a leading determinant of hypertension, dyslipidaemia, and diabetes mellitus. A generally favourablelipid profile (low total and LDL cholesterol, and normal to high HDL cholesterol) and low homocysteine values have been reported among the general population in Africa[104] However, hyperlipidaemia is becoming increasingly common, and studies from Tanzania observed 25% prevalence of elevated serum total cholesterol (cholesterol > 5.2 mmol/L)[105] and 15% prevalence of elevated triglycerides (TG ≥ 1.7 mmol/L) among adults over 35 years of age, with women being affected more than men.

Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century. Obesity is stigmatized in much of the modern world (particularly in the Western world), though it was widely perceived as a symbol of wealth and fertility at other times in history, and still is in some parts of the world. Most individuals with type 2 diabetes exhibit abdominal obesity which itself causes insulin

resistance. Abdominal obesity measured by waist/hip ratio (WHR) has been implicated as carrying more risk for type 2 diabetes than peripheral fat distribution.[101,104]

Dieting and physical exercise are the mainstays of treatment for obesity. Diet quality can be improved by reducing the consumption of energy-dense foods such as those high in fat and sugars, and by increasing the intake of dietary fiber. Anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption together with a suitable diet. If diet, exercise and medication are not effective, a gastric balloon may assist with weight loss, or surgery may be performed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food.

1.7.3: Physical inactivity

Physical inactivity is a well-known risk factor for type 2 diabetes. The risk of diabetes is reduced by 50% among men who take moderately vigorous exercise.It has been shown in a prospective study that physical activity is inversely related to the prevalence of diabetes. Occupation is not a good indicator of physical activity as measurement of energy expenditure in kilocalories or metabolic equivalents (METS).[105,106]

1.7.4: Alcohol consumption

Heavy consumption of alcohol has been positively associated with diabetes.[107] This may be due to hepatic and/or pancreatic damage, which is known to complicate alcoholism.[108]Some studies in Enugu have reported association between liver disease and diabetes in Nigeria.[109,110] Moderate drinking reduces the risk of diabetes by improving insulin sensitivity.[105]Moderation is advised with regard to consuming alcohol and the use of some drugs. Alcohol inhibits glycogenesis in the liver and some drugs inhibit hunger symptoms. This, together with impaired judgment, memory and concentration caused by some drugs can lead to hypoglycemia.

Diabetics who take insulin or tablets such as sulphonylureas should not, therefore, ever consume alcohol on an empty stomach, but take some starchy food (such as bread or potato crisps) at the same time as consumption of alcohol.

1.7.5: Tobacco use

Tobacco use leads most commonly to diseases affecting the heart and lungs, with smoking being a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (COPD), emphysema, and cancer (particularly lung cancer, cancers of the larynx and mouth, and pancreatic cancer). Cigarette smoking increases the risk of Crohn's disease as well as the severity of the course of the disease. It is also the number one cause of bladder cancer. The smoke from tobacco elicits carcinogenic effects on the tissues of the body that are exposed to the smoke. Tobacco smoke can combine with other carcinogens present within the environment in order to produce elevated degrees of lung cancer. The World Health Organizationestimate that tobacco caused 5.4 million deaths in 2004 and 100 million deaths over the course of the 20th century. Similarly, the United States Centers for Disease Control and Prevention describes tobacco use as "the single most important preventable risk to human health in developed countries and an important cause of premature death worldwide."[111]

1.7.6: Family history

It is well accepted that the lifetime risk of any offspring developing diabetes is about 40% if one parent has diabetes and 70% if both parents have diabetes.[111,112] Family history of diabetes is more frequently obtained from diabetic subjects than from non-diabetic individuals. Omar and Asmal[115] and Mengesha et al. [116]Studies have highlighted the importance of family history of diabetes in South Africa and Ethiopia, respectively.[113,114] The National survey in Nigeria also reported that subjects with diabetic parents were at increased risk of having diabetes.[107]

1.7.7: Advancing age

Advancing age was another identified independent risk factor for diabetes, which was more prevalent in subjects aged 50 years and above. It has been found that the peak incidence of diabetes in Nigeria and Tanzania, respectively, was after 45-50 years of age. [117,118] It is well known that the prevalence of diabetes increases with age.[117] In Nigeria, the risk of diabetes increases 3-4-folds after the age of 44 years.[108] The worsening of

insulin resistance with age and increasing longevity of diabetic patients due to improved care, all contribute to the rising prevalence of type 2 diabetes with age.[117,118]

1.8 OBJECTIVES OF THE STUDY

General

To assess the prevalence of type 2 diabetes and to determine potential associated risk factors of the disease in University of Nigeria Nsukka.

Specific

To evaluate some risk factors of diabetes mellitus such as hypertension, obesity, alcohol consumption and physical inactivity.

To educate participants on Self-monitoring of blood glucose (SMBG).

To counsel and advice participants on medication adherence and lifestyle modification.

CHAPTER TWO
METHODS

2.1 STUDY DESIGN

This was a prospective, cross sectional household study in University of Nigeria Nsukka Staff quarters.

2.2 STUDY AREA

The University of Nigeria, commonly referred to as UNN, is a federal university located in Nsukka, Enugu State, South Eastern Nigeria. Founded in 1955 and formally opened on 7 October 1960, the University of Nigeria has four campuses – Nsukka, Enugu and Ituku-Ozalla – located in Enugu State and one in Aba, Abia State, Nigeria. The University of Nigeria was the first full-fledged indigenous and first autonomous university in Nigeria, modeled upon the American educational system. It is the first land-grant university in Africa and one of the five elite universities in the country. The university has 15 Faculties and 102 academic departments. The University offers 82 undergraduate programmes and 211 postgraduate programmes.[119]There are also institutes, units, and centres in the University.

2.3 STUDY POPULATION

This survey was carried out using the Staff quarters located within University of Nigeria Nsukka campus. There is about 590 households in the campus. Many ethnic groups and tribes in Nigeria are in the university but major ethnic group is Igbo because the university is sited in Igbo speaking part of Nigeria. Expatriates, professional and researchers from different parts of the world also live in University of Nigeria Nsukka. The quarters are well planned, which made sampling and logistics for the study easier.

2.4 SAMPLING PROCEDURES

All households in the Staff quarters located within University of Nigeria Nsukka campus were enlisted for the study. Any member of a household who agreed to participate and fulfilled the inclusion criteria was selected for the survey. All participants signed a

consent form and was given a handbill designed for the survey, explaining the purpose, benefits, instructions, what participants are expected do and dates of the study. The study was carried out only in the evenings and weekends to make sure that the members of the households were around since most of them are either civil servants or students.

2.5 METHOD OF DATA COLLECTION AND STUDY PROCEDURE

A data collection form designed for the study based on the objectives of the study was used to collect necessary data for all the participants. Socio-demographic data and history of personal habits such as smoking, alcohol consumption and physical activity were obtained.

Physical activity was assessed from the leisure sports and occupation of the individual. People who engaged in manual labour, such as farming or professional sports were classified as physically active, while those who engaged in trade, housework or nursing were classified as moderately active physically. Physically inactive people included those who did sedentary jobs, e.g. office workers, or the unemployed. Those who engaged in sedentary jobs were classified as moderately active physically if they engaged in leisure sports.

Alcohol consumption was categorized as moderate or heavy based on the criteria of the Royal College of Physicians of London.[120] Alcohol intake of 21 units/week or more was regarded as heavy drinking (one bottle of Nigerian lager beer contains 2.4-3 units of alcohol, therefore taking more than 7 bottles of beer per week was considered as heavy drinking), while less than 21 units/week (< 7 bottles/week) was regarded as moderate drinking.[120]

Physical examination was carried out by the investigators. The weight and height of the subject was measured to the nearest kilogram with a Hanson type bathroom weighing scale and to the nearest meter respectively. The body mass index (BMI) was calculated and the classification done according to the recommendations of the WHO expert committee for the classification of overweight.[121]

The waist and hip circumference were measured with a flexible tape to the nearest 0.5 cm wearing minimal clothing; the waist/hip ratio (WHR) was then calculated and recorded.

Blood pressure was taken from the nondominant arm after 10 minutes of rest using appropriate cuff size and a mercury sphygmomanometer. Systolic blood pressure (SBP) and diastolic blood pressures (DBP) were the first and fifth Korotkoff sounds, respectively. The mean of three readings, five minutes apart, was determined. Hypertension was defined as SBP greater than or equal to 140 mmHg and/or DBP equal to or greater than 90 mmHg.[122] Hypertension was classified thus: (i) mild: SBP 140–159 mmHg and/or DBP 90–99 mmHg; (ii) moderate: SBP 160–179 mmHg and/or DBP 100–109 mmHg; (iii) severe: SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg.

Random blood sugar (RBS) of all the participants was measured using accu check active glucometer. FPG of all participants who had RBS levels ≥ 200 mg/dl was measured. Participants who had FPG levels ≥126 mg/dl (7.0 mmol/l) were subjected to a 75 g oral glucose tolerance test (OGTT) as soon as possible during the study period, with sampling at 0 and 2 h after glucose load.

2.6 INCLUSION CRITERIA

1) Age, 45 years and above. 2) Age less than 45 if the participant has BMI ≥ 25 kg/m^2.
3) Resident in the University of Nigeria Nsukka staff quarters.
5) Willing to participate and comply with the instructions of the study. 6) Informed consent.

2.7 EXCLUSION CRITERIA

1) History of use of drugs that could affect glucose metabolism e.g. steroids, B-blockers, thiazide diuretics. 2) Pregnant women.

2.8 CRITERIA FOR DATA INTERPRETATION

Diabetes is defined according to WHO criteria of 1999.[23] Individuals who were previously known to have diabetes based on history and laboratory data were also classified as having diabetes without OGTT.

2.9 CRITERIA FOR THE DIAGNOSIS OF DIABETES[23]

1. Symptoms of diabetes and the classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

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

OR

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

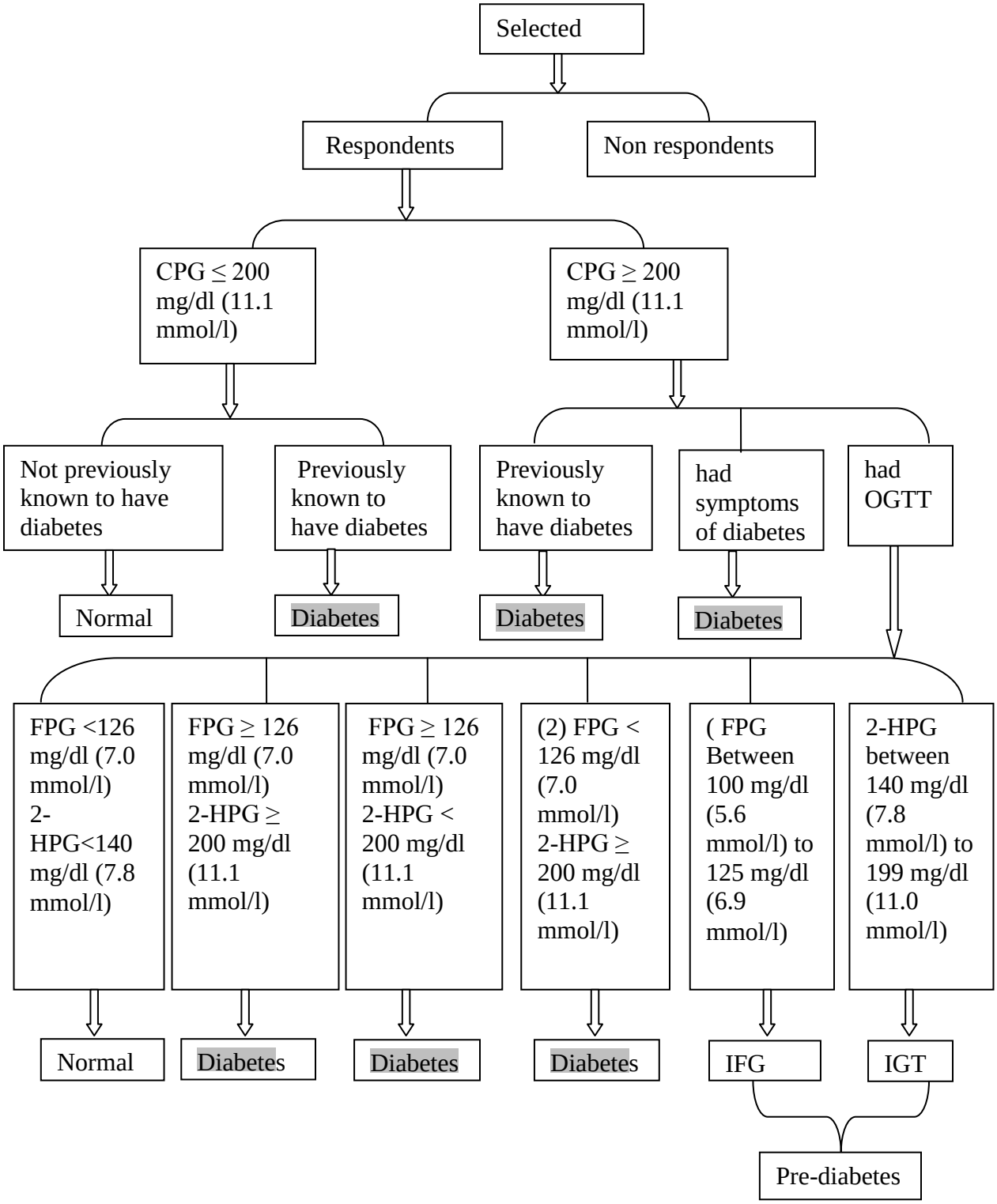

Fig 2.1: Diagrammatic Presentation of Study Procedure

2.10 Statistical Analysis

The data obtained were coded, entered and analysed using SPSS version16. The data were presented as mean ±/S.D. Comparison was done by Student's t -test for continuous variable and Chi Square-test for discrete variables. All diabetes risk factors were entered into a multivariate logistic regression model, with diabetes (0 = no, 1 = yes) as the dependent variable. BMI, WHR and age are continuous variables and the others are categorical.

2.11 Ethical Consideration

This study was conducted with adherence to ethical standards. Informed consent and approval for this study was obtained from the participants and Ethics Committee of University medical center respectively and confidentiality was maintained.

CHAPTER THREE

RESULTS

Two Hundred and Four (204)staff participated in the survey. Two categories were made from the staff: staff category 1 (comprising 157 senior staff and 47 junior staff) (Table 3.1) and staff category 2 (comprising 100 academic staff, 80 administrative staff and 24 technical staff) (Table 3.2). The data of participants are given below:

3.1. Sex and age distribution

The subjects were aged from 30 years and above. For category 1, the male to female ratio was: 1.2:1 for senior and 1:5.7 for junior staff (Table 3.1); and for category 2: 1:1.27 for academic, 1:2.48 for administrative and 1:1.4 for technical staff (Table 3.2). Senior staffs were significantly older than junior staff (Table 3.1) and academic staffs were significantly older than administrative and technical staff (Table 3.2).

3.2. Marital status and education

96.1% of the staff was married, 2.5% and 1.5% widowed and single respectively. 89.7%, 6.4%, 2% and 2% had tertiary, secondary, primary and no formal education respectively (Table 3.1 and 3.2).

Table 3.1.Demographic data of senior and junior staff (staff category 1)

Characteristics	Senior	Junior	Total
Gender			
Male	70(34.3)	7(3.4)	77(37.7)
Female	87(42.6)	40(19.6)	127(62.3)
Age (yr)			
30-40	26(12.7)	17(8.3)	43(21.1)
41-50	69(33.8)	14(6.9)	83(40.7)
51-60	42(20.6)	11(5.4)	53(26.0)
>60	20(9.8)	5(2.5)	25(12.3)
Marital status			
Married	152(74.5)	44(21.6)	196(96.1)
Single	2(1.0)	1(0.5)	3(1.5)
Widowed	3(1.5)	2(1.0)	5(2.5)
Education			
No formal education	1(0.5)	3(1.5)	4(2.0)
Primary	0(0.0)	4(2.0)	4(2.0)
Secondary	4(2.0)	9(4.4)	13(6.4)
Tertiary	152(74.5)	31(15.2)	183(89.7)

Table 3.2.Demographic data of academic, administrative and technical staff (staff category 2)

Characteristics	Academic	Administrative	Technical	Total
Gender				
Male	44(21.6)	23(11.3)	10(4.9)	77(37.7)
Female	56(27.5)	57(27.9)	14(6.9)	127(62.3)
Age (yr)				
30-40	20(9.8)	17(8.3)	6(2.9)	43(21.1)
41-50	42(20.6)	36(17.6)	5(2.5)	83(40.7)
51-60	23(11.3)	22(10.8)	8(3.9)	53(26.0)
>60	15(7.4)	5(2.5)	5(2.5)	25(12.3)
Marital status				
Married	96(47.1)	77(37.7)	23(11.3)	196(96.1)
Single	1(0.5)	2(1.0)	0(0.0)	3(1.5)
Widowed	3(1.5)	1(0.5)	1(0.5)	5(2.5)
Education				
No formal education	3(1.5)	0(0.0)	1(0.5)	4(2.0)
Primary	0(0.0)	3(1.5)	1(0.5)	4(2.0)
Secondary	1(0.5)	7(3.5)	5(2.5)	13(6.4)
Tertiary	96(47.1)	70(34.3)	17(8.3)	183(89.7)

3.3. Co morbidities

About 29.9% of the staff were hypertensive, 15.7% have arthritis, 10.3% have peptic ulcer and 6%, 3% and 2% have stroke, hypercholesterolemia and CHF respectively (Table 3.3 and 3.4).

Table 3.3: Co morbidities forsenior and junior staff(staff category 1)

Co morbidities	Senior	Junior	Total
Hypertension	44(21.6)	17(8.3)	61(29.9)
Arthritis	23(11.3)	9(4.4)	32(15.7)
CHF	2(1.0)	0(0.0)	2(1.0)
Hypercholesterolemia	3(1.5)	0(0.0)	3(1.5)
Stroke	3(1.5)	3(1.5)	6(2.9)
Peptic ulcer	17 (8.3)	4(2.0)	21(10.3)
No of co morbidities			
0	91(44.6)	21(10.3)	112(54.9)
1	46(22.5)	18(8.8)	64(31.3)
2	17(8.3)	8(3.9)	25(12.2)
3	2(1.0)	0(0.0)	2(1.0)
4	1(0.5)	0(0.0)	1(0.5)

Table 3.4: Co morbidities of academic, administrative and technical staff (staff category 2)

Co morbidities	Academic	Administrative	Technical	Total
Hypertension	31(15.2)	20(9.8)	10(4.9)	61(29.9)
Arthritis	14(6).9	14(6.9)	4(2.0)	32(15.7)
CHF	1(0.5)	1(0.5)	0(0.0)	2(1.0)
Hypercholesterolemia	2(1.0)	1(0.5)	0(0.0)	3(1.5)
Stroke	3(1.5)	1(0.5)	2(1.0)	6(2.9)
Peptic ulcer	11(5.4)	8(3.9)	2(1.0)	21(10.3)
No of co morbidities				
0	55(27.0)	45(22.1)	12(5.9)	112(54.9)
1	31(15.2)	27(13.2)	6(2.9)	64(31.3)
2	13(6.4)	6(2.9)	6(2.9)	25(12.2)
3	0(0.0)	2(1.0)	0(0.0)	2(1.0)
4	1(0.5)	0(0.0)	0(0.0)	1(0.5)

3.4. Anthropometry

BMI was computed using the standard formula of weight (kg)/height (m^2). BMI <18.5 as underweight, 18.5 to 24.99 as normal, 25 to 29.99 as overweight and ≥30 kg as general obesity were used. The mean BMI for category 1 was 30.123 ± 5.080 for senior and 29.588 ± 5.671 for junior staff; and for category 2: 30.827 ± 4.915 for academic, 29.006 ± 5.476 for administrative and 29.863 ± 5.141 for technical staff (Table 3.5). In total, 82.4% of the staff had BMI >25 kg/m2 while 76.5% had waist girth >35cm (Table 3.6 and 3.10).

3.5. Weight and blood pressure

The mean weights for senior, junior, academic, administrative and technical staff were 82.417 ± 16.196, 78.155 ± 15.639, 84.930 ± 15.778, 77.856 ± 15.525 and 78.804 ± 17.102 respectively. The mean SBP for senior, junior, academic, administrative and technical staff were 139.516 ± 19.800, 138.447 ± 20.276, 142.880 ± 20.384, 133.738 ± 18.195 and 142.667 ± 19.553 respectively while that of DBP were 80.535 ± 12.037, 78.723 ± 9.859, 81.830 ± 11.433, 79.550 ± 11.40 and 75.708 ± 11.911 respectively (Table 3.5).

Table 3.5: Laboratory values for all staff categories(staff category 1 and 2)

Characteristics *Laboratory values*	Senior	Junior	Academic	Administrative	Technical
Weight (mean±sd)	82.42 ± 16.20	78.16±15.64	84.930±15.78	77.86 ±15.53	78.80 ±17.10
BMI (mean±sd)	30.12± 5.08	29.59±5.67	30.83 ±4.92	29.01 ±5.48	29.863±5.14
SBP (mean±sd)	139.52 ±19.80	138.45±20.28	142.880±20.38	133.74±18.20	142.67 ±19.55
DBP(mean±sd)	80.54 ±12.04	78.72 ±9.86	81.83 ±11.43	79.55 ±11.40	75.71±11.91
RBS (mean±sd)	121.37 ±31.69	129.34 ±36.88	124.67 ±32.59	119.80 ±28.19	128.46 ±47.43

3.6. Family history of diabetes

Family history of diabetes was identified in 60 staff (29.4%) (Table 3.6, 3.10 and 3.11); 17 of these (8.3%) had diabetic fathers, while 21 (10.3%) of them had mothers with diabetes. 22 subjects (10.8%) had relations who had diabetes (brothers and sisters).

3.7. Plasma glucose

The plasma glucose profiles of the subjects are summarized in Tables 3.8 and 3.9. 5(2.5%) of the staff had RBS >200mg/dl and all of these were previously known to have diabetes and so were classified as having diabetes without OGTT and FBS. And thus FBS and OGTT were not carried out.

3.8. Prevalence of diabetes

The overall prevalence of diabetes in this study was 9.8%. At the time of visit, 1.5% and 1% of the senior staff and the junior staff respectively had RBS >200mg/dl but 6.4% and 3.4% of the senior staff and the junior staff respectively were known diabetics (Table 3.8). And 0.5%, 1% and 1% of the academic, administrative and technical staff respectively had RBS >200mg/dl but 3.9%, 2.9% and 2.9% of the academic, administrative and technical staff respectively were known diabetics (Table 3.9). The mean RBS concentrations for the senior, junior, academic, administrative and technical staff were 121.37 ± 31.69, 129.34 ± 36.88, 124.67 ± 32.59, 119.80 ± 28.19 and 128.46 ± 47.43 respectively (Table 3.5). There was no significant difference between the glycemic indices for the junior staff and the senior staff and between academic, administrative and technical staff, $p > 0.05$. The mean diabetes risk score were 58.50 ± 14.99, 54.68 ± 16.53, 57.75 ± 14.50, 57.38 ± 16.74, 57.92 ± 15.03 for senior, junior, academic, administrative and technical staff respectively (table 3.5). Of the total population studied, 114 (55.4%) subjects go for routine glycemic/glucosuriccheck up and they were essentially those who were known diabetic (Table 3.10 and 3.11).

Table 3.6: Risk factors of all staff categories(staff category 1 and 2)

Risk factors	Senior	Junior	Academic	Administrative	Technical	Total
Hypertension (known)	44(21.6)	17(8.3)	31(15.2)	20(9.8)	10(4.9)	61(29.9)
Waist girth (>35cm)	123(60.3)	33(16.3)	81(39.1)	60(29.4)	15(7.4)	156(76.5)
BMI (kg/m2)						
Overweight	57(27.9)	15(7.4)	39(19.1)	27(13.2)	6(2.9)	72(35.3)
Obese	73(35.8)	23(11.3)	51(25.0)	33(16.2)	12(5.9)	96(47.1)
BMI (mean±SD)	30.123 ±5.080	29.588±5.671	30.827±4.915	29.006 ±5.476	29.863±5.141	
Physical inactivity	28(13.7)	7(3.4)	16(7.8)	13(6.4)	6(2.9)	35(17.2)
Family history	48(23.5)	12(5.9)	29(14.2)	29(14.2)	2(1.0)	60(29.4)
Alcohol	65(32.7)	18(9.0)	38(19.1)	34(17.1)	11(5.5)	83(41.7)
Smoking	5(2.5)	1(0.5)	4(2.0)	2(1.0)	0(0.0)	6(2.9)

3.9. Risk factors for diabetes

- Obesity: 72(35.3%) and 91(46.1%) of the total population were overweight and obese respectively (Table 3.6). 156(76.5%) of the total participants have their waist girth >35 cm (Table 3.6, 3.10 and 3.11). Both do not influence seem to influence prevalence of diabetes.

- Hypertension: 61(29.9%) of the total population were known hypertensive (Table 3.6). Hypertension appeared not to be an important factor influencing the prevalence of diabetes.

- Physical inactivity: In this study, physical inactivity appeared not to be an important factor influencing the prevalence of diabetes in people previously known to have diabetes as 35(17.2%) of the total population do not engage in any form of exercise (Table 3.6, 3.10and 3.11).

- Family history of diabetes: 60 (29.4%) of the total participants have diabetes (Table 3.6). Family history of diabetes showed influence on the prevalence of diabetes in this study (Table 3.7) as diabetes was significantly more prevalent in people with a family history of diabetes compared with those without a family history.

- Alcohol: 83(41.7%) of the total participants take alcohol (Table 3.6). Participants who drank more than 21 units of alcohol per week were not more likely to have diabetes than those who drank moderately (Table 3.7).

- Smoking: 6(2.9%) of the total participants smoke (Table 3.6). Smoking showed no influence on the prevalence of diabetes in this study (Table 3.7).

Table 3.7: Correlation tableof all staff categories(staff category 1 and 2)

Characteristics	General	Senior	Junior	Academic	Administrative	Technical
CAT RBS	.481	.465	.504		.562	.552
RBS	.293	.219	.476		.305	.584
Risk factors						
Blood pressure				.215		
CHF				.341		
Peptic ulcer					.221	
Alcohol intake	-.238	-.221	-.322	-.251		
No of bottles per week	-.216	.228		.381		
Family history			.303		.522	.552
Weight lose advice				.198		
Health status	.169			.352	.355	.441
No of drugs	.374	.316	.460	.352		

Table 3.8: Percentage distribution of diabetes among senior and junior staff (staff category 1)

Characteristics	Senior	Junior
RBS		
Normal	154(75.5)	45(22.1)
Diabetes	3(1.5)	2(1.0)
Impression		
Normal	144(70.6)	40(19.6)
Diabetes	13(6.4)	7(3.4)
Diabetes risk score		
Low	68(33.3)	23(11.3)
Moderate	70(34.3)	20(9.8)
High	19(9.3)	4(2.0)

Table 3.9: Percentage distribution of diabetes among of academic, administrative and technical staff (staff category 2)

Characteristics	Academic	Administrative	Technical
RBS			
Normal	99(48.5)	78(38.2)	22(10.8)
Diabetes	1(0.5)	2(1.0)	2(1.0)
Impression			
Normal	92(45.1)	74(36.3)	18(8.8)
Diabetes	8(3.9)	6(2.9)	6(2.9)
Diabetes risk score			
Low	48(23.5)	33(16.2)	10(4.9)
Moderate	39(19.1)	39(19.1)	12(5.9)
High	13(6.4)	8(3.9)	2(1.0)

Table 3.10: Risk factor assessment for senior and junior staff (staff category 1)

Risk factors assessment	Senior	Junior	Total
Knowledge			
Do you believe that diabetes has no cure?	73(36.0)	24(11.8)	97(47.8)
Do you think maintaining a healthy weight is necessary	145(71.1)	40(19.6)	185(90.7)
Behavior			
Have you ever gone for diabetes screening before now?	95(46.6)	19(9.3)	114(55.4)
Have you been advised by any health professional to lose weight?	77(37.7)	28(13.7)	105(55.5)
How often do you consciously eat fruits and vegetables			
Everyday	107(52.5)	23(11.3)	130(63.7)
Once in a while	43(21.1)	23(11.3)	66(32.4)
Not at all	7(3.4)	1(0.5)	8(3.9)
Risk			
Waist girth(inches)			
<31	2(1.0)	3(1.5)	5(2.5)
31-35	32(15.7)	11(5.4)	43(21.1)
>35	123(60.3)	33(16.3)	156(76.5)
Do you consume alcoholic drinks?			
Current drinker	65(32.7)	18(9.0)	83(41.7)
Ex drinker	21(10.6)	4(2.0)	25(12.6)
Never drinker	66(33.2)	25(12.6)	91(45.7)
On the average, how many bottles of alcohol do you take in a week?			
<7	69(68.3)	19(18.8)	88(87.1)
7-12	4(4.0)	0(0.0)	4(4.0)
12-24	7(6.9)	1(1.0)	8(7.9)
>24	1(1.0)	0(0.0)	1(1.0)
Do you smoke?			
Current smoker	5(2.5)	1(0.5)	6(2.9)
Ex smoker	8(3.9)	1(0.5)	9(4.4)
Never smoker	144(70.6)	45(22.1)	189(92.6)
Has any one of your parents been diagnosed with diabetes?			
One	40(19.6)	10(4.9)	50(24.5)
Both	8(3.9)	2(1.0)	10(4.9)
None	109(53.4)	35(17.3)	144(70.6)
Family history of diabetes	48(23.5)	12(5.9)	60(29.4)

Table 3.10: Risk factor assessment for senior and junior staff (staff category 1)

Which of these sets of food do you eat often?			
Starch	80(39.2)	23(11.3)	103(50.5)
Protein	36(17.6)	18(8.8)	54(26.5)
Fat 1(plant fat)	8(3.9)	1(0.5)	9(4.4)
Fat 2 (animal fat)	8(3.9)	0(0.0)	8(3.9)
Fruits and vegetables	25(12.3)	5(2.5)	30(14.7)
Risk / Behavior			
How often do you take part in exercise?			
Regular/Everyday	44(21.6)	20(9.8)	64(31.4)
Moderate/<3days per wk	20(9.8)	5(2.5)	25(12.3)
Mild/Once a while	65(31.9)	15(7.4)	80(29.3)
None / sedentary	28(13.7)	7(3.4)	35(17.2)

(Numbers represent participants that answered yes/agreed to the questions).

Table 3.11: Risk factor assessment for of academic, administrative and technical staff (staff category 2)

Risk factors assessment	Academic	Administrative	Technical	Total
Knowledge				
Do you believe that diabetes has no cure?	45(22.2)	39(19.3)	13(6.4)	97(47.8)
Do you think maintaining a healthy weight is necessary	91(44.6)	73(35.8)	21(10.3)	185(90.7)
Behavior				
Have you ever gone for diabetes screening before now?	61(29.9)	39(19.1)	14(6.9)	114(55.4)
Have you been advised by any health professional to lose weight?	54(26.5)	38(18.6)	13(6.4)	105(55.5)
How often do you consciously eat fruits and vegetables?				
Everyday	70(34.3)	47(23.0)	13(6.4)	130(63.7)
Once in a while	27(13.2)	29(14.2)	10(4.9)	66(32.4)
Not at all	3(1.5)	4(2.0)	1(0.5)	8(3.9)
Risk				
Waist girth(inches)				
<31	3(1.5)	1(0.5)	1(0.5)	5(2.5)
31-35	16(7.8)	19(9.3)	8(3.9)	43(21.1)
>35	81(39.1)	60(29.4)	15(7.4)	156(76.5)
Do you consume alcoholic drinks?				
Current drinker	38(19.1)	34(17.1)	11(5.5)	83(41.7)
Ex drinker	14(7.0)	7(3.5)	4(2.0)	25(12.6)
Never drinker	44(22.1)	38(19.1)	9(4.5)	91(45.7)
On the average, how many bottles of alcohol do you take in a week?				
<7	42(41.6)	36(35.6)	10(9.9)	88(87.1)
7-12	3(3.0)	1(1.0)	0(0.0)	4(4.0)
12-24	5(5.0)	2(2.0)	1(1.0)	8(7.9)
>24	1(1.0)	0(0.0)	0(0.0)	1(1.0)
Do you smoke?				
Current smoker	4(2.0)	2(1.0)	0(0.0)	6(2.9)
Ex smoker	6(2.9)	2(1.0)	1(0.5)	9(4.4)
Never smoker	90(44.1)	76(37.3)	23(11.3)	189(92.6)
Has any one of your parents been diagnosed with diabetes?				
One	26(12.7)	22(10.8)	2(1.0)	50(24.5)
Both	3(1.5)	7(3.4)	0(0.0)	10(4.9)
None	71(34.8)	51(25.0)	22(10.8)	144(70.6)
Family history of diabetes	29(14.2)	29(14.2)	2(1.0)	60(29.4)

(continued)

Table 3.11: Risk factor assessment for of academic, administrative and technical staff (staff category 2)

Which of these sets of food do you eat often?				
Starch	50(24.5)	39(19.1)	14(6.9)	103(50.5)
Protein	24(11.8)	23(11.3)	7(3.4)	54(26.5)
Fat 1(plant fat)	7(3.4)	2(1.0)	0(0.0)	9(4.4)
Fat 2 (animal fat)	6(2.9)	2(1.0)	0(0.0)	8(3.9)
Fruits and vegetables	13(6.4)	14(6.9)	3(1.5)	30(14.7)
Risk / Behavior				
How often do you take part in exercise?				
Regular/Everyday	34(16.7)	23(11.3)	7(3.4)	64(31.4)
Moderate/<3days per wk	14(6.9)	9(4.4)	2(1.0)	25(12.3)
Mild/Once a while	36(17.6)	35(17.2)	9(4.4)	80(29.3)
None / sedentary	16(7.8)	13(6.4)	6(2.9)	35(17.2)

(Numbers represent participants that answered yes/agreed to the questions).

CHAPTER FOUR

4.1 DISCUSSION

The prevalence rate of type 2 diabetes in this cross sectional study was 9.8%. This is close to the rate of 7.2% reported for the Lagos mainland by the National non-communicable disease survey.[107] Although the National standardized rate is 2.2% in Nigeria, the crude prevalence rate is 7.4% in those aged 45 years and above who live in urban areas.[107] However, it is noteworthy that other cities in Nigeria have lower rates than that in Nsukka. For instance, Ibadan, had prevalence rates of 1.5% in the National survey[108] and 0.8% in another study.[123] Jos, had a prevalence rate of 3.1%.[124] Although these studies included younger age groups, the wide difference observed may not be explained by age alone. Lagos and Port Harcourt are among the most industrialized cities in Nigeria. This might explain the similarity in prevalence rates observed in the two areas. Modernization, overweight, obesity, physical lifestyle and dietary changes could explain to some extent, the high prevalence rate obtained in this study.

The prevalence of type 2 diabetes in this study (9.8%) is at variance with 23.4%, which was reported among oil workers in Port-Harcourt Nigeria.[125] and the associated factors were affluent diet comprising of a high fat consumption and reduced complex carbohydrate besides sedentary life style.[126] This might be attributed to higher level of education, awareness of diabetes and its risk factors and routine check in the study population. Most of the known diabetics had their blood sugar controlled as their RBS were within normal range (<200mg/dl). The devastating sequelae of an untreated case cannot be over emphasized.

The study revealed that routine glycemic/glucosuric checkup is moderately popular in Nigeria as 50.2% go for routine checkup which is at variance with 5.9% reported among oil workers in Port-Harcourt Nigeria.[125]

Prevalence of diabetes mellitus in various countries has been reported, and this varies considerably around the world.[127] Therefore, no matter what the prevalence may be it should not be taken with levity both at curative and preventive levels.

Some proven and hypothesized risk factors were examined to evaluate their associations with type 2 diabetes in this study population. The findings of this study are in accordance with what has been known about obesity and diabetes. Obesity is by far the strongest modifiable risk factor for type 2 diabetes.[128,129] Subjects with BMI >25 kg/m2 and waist girth >35cm were at significantly higher risk of having type 2 diabetes. Other epidemiological studies have demonstrated this effect of obesity on diabetes.[130] Multivariate analysis showed family history of diabetes and hypertension as risk factors for type 2 diabetes in this population. It is well accepted that the lifetime risk of any offspring developing diabetes is about 40% if one parent has diabetes and 70% if both parents have diabetes.[131,132]

Family history of diabetes is more frequently obtained from diabetic subjects than from non-diabetic individuals. Studies have highlighted the importance of family history of diabetes in South Africa and Ethiopia, respectively.[113,133] The National survey in Nigeria also reported that subjects with diabetic parents were at increased risk of having diabetes.[108] While these support the effect of heredity on the prevalence of diabetes, they also raise the issue of ascertainment bias, since individuals with diabetes are more likely to be aware of history of diabetes in their parents than non diabetic subjects.

Heavy consumption of alcohol has been positively associated with diabetes.[107]This may be due to hepatic and/or pancreatic damage, which is known to complicate alcoholism.Studies in Enugu have reported association between liver disease and diabetes in Nigeria. [134,135] Moderate drinking reduces the risk of diabetes by improving insulin sensitivity,[105,136] this may explain the lack of association between diabetes and drinking when both moderate and heavy drinkers were analyzed together against abstainers. Physical inactivity is a well-known risk factor for type 2 diabetes.

The risk of diabetes is reduced by 50% among men who take moderately vigorous exercise.[105] A prospective study showed that physical activity is inversely related to the prevalence of diabetes.[105,126] This study found an association between physical inactivity and diabetes in people who were previously known to have diabetes; however, this association was not sustained when all the diabetic subjects were analyzed together. This lack of association might be a reflection of the non-standardized indices used for measuring physical activity.

Occupation is not a good indicator of physical activity as measurement of energy expenditure in kilocalories or metabolic equivalents (METS), but it was not feasible to use the latter in this study because most of the subjects did not engage in leisure sports. Senior staff had a significantly higher prevalence of type 2 diabetes than those in the junior staff. This finding agrees with the observation by Indian Doctors in 400 BC that diabetes was a disease of the rich. Zimmet also noted that diabetes was more common in the upper-class families in the developing Nations of the world.[137]Although there is a fundamental distinction between the senior staff and junior staff in term of socioeconomic status, this distinction however did not reflect in their body mass indices ($P > 0.05$) correspondingly. There was also no statistical difference in the prevalence of diabetes between the junior staff and senior staff. The seemingly equilibration of body mass/diabetic indices between these two categories of staff might be due to the fact that this study was done in a semi urban area where traditional life style takes preeminence over westernization. Here affordability/accessibility to traditional diet might not necessarily be a function of one's socioeconomic status, as supply is usually enormous. This study has shown that traditional diet can moderate body mass index with a concomitant reduction in the prevalence of diabetes.

4.2: LIMITATION OF STUDY

Most of the staff of University of Nigeria Nsukka where the study was carried out refused to participate in the study as many of them claim knowledge of their health status (diabetes). Most of the staff who have diabetes refused to participate in the study also claiming that they check their blood sugar regularly. Some of the staff were afraid of the

needle prick for blood sugar examination so they refused to participate in the study. All these contributed tofew number of respondents. The study was disturbed by rain since the study was carried out during the rainy season.

4.3: COUNCLUSION

This study established that the prevalence of type 2 diabetes in University of Nigeria Nsukka staff quarters was fairly high (9.8%). Some of the identified risk factors for type 2 diabetes were hypertension, obesity and family history most of which are modifiable, making type 2 diabetes a potentially preventable disease. It would be prudent, therefore, to recommend screening of subjects at risk and lifestyle modification to reduce the prevalence of type 2 diabetes. However, routine checkup for diabetes is remarkably good, need for awareness programmes emphasizing the need for traditional diet besides routine glycemic/glucosuric checkup is necessary. Epidemiological evidence suggests that without effective prevention and control programmes, the burden of diabetes is likely to continue to increase globally. Routine fasting/random blood sugar (glycemic) and glucosuric (urinalysis) remain important panacea for early detection of diabetes and its management.

4.4: RECOMMENDATIONS

1. There is great need for awareness programmes on the need to allow researches such as this to be carried out in the University community and the villages around may benefit more.

2. Patient education, understanding, and participation is vital, since the complications of diabetes are far less common and less severe in people who have well-managed blood sugar levels.

3. More of this study should be done in the rural area where level of education and awareness are low. There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds.

4. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

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APPENDIX

Appendix 1:

Invitation to participate in study (the information for the participant)

This is to invite individuals who will consent to participate in a study titled, "Prevalence of Type 2 Diabetes Mellitus in a University Community Staff Quarters" in Nigeria. This study is purely for academic purpose.

Involvement in the study is strictly **VOLUNTARY** and requires each participant to sign an **INFORMED CONSENT FORM (See below).**

WHAT IS DIABETES MELLITUS?

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia; is associated with abnormalities in carbohydrate, fat and protein metabolism; and results in chronic complications including microvascular, macrovascular, and neuropathic disorders.This has been attributed in part to increasing obesity, sedentary lifestyle, and eating habits. Hyperglycemia is a common end point for all types of diabetes mellitus and is the parameter that is measured to evaluate and manage the efficacy of diabetes therapy.

PURPOSE OF STUDY

MAIN OBJECTIVE:

To evaluate the prevalence of type 2 diabetes mellitus in University of Nigeria Nsukka.

SPECIFIC OBJECTIVES:

- To evaluate some risk factors of diabetes mellitus such as hypertension, obesity, alcohol consumption and physical inactivity.

- To identify factors that predispose the respondents to diabetes.

WHO IS ELIGIBLE TO PARTICIPATE: Those who are eligible to participate are individuals living in staff quarters of the university who are 45 years and above and/or having BMI $\geq$ 25 kg/m^2.

The **inclusion criteria** are:

1) Age, 45 years and above. 2) Age less than 45 if the participant has BMI $\geq$ 25 kg/m^2.

3) Resident in the University of Nigeria Nsukka staff quarters.

4) Willing to participate and comply with the instructions of the study e.g. overnight fasting where necessary.

5) Giving consent to participate in the study.

Exclusion Criteria

1) History of use of drugs that could affect glucose metabolism e.g. steroids, B-blockers, thiazide diuretics. 2) Pregnant women.

STUDY DESIGN:

The study would be a longitudinal household study. Households will be selected systematically (every other household)

Number of visits to household: The researcher will visit each household for 1 to 3 times.

PROPOSED REQUIREMENTS FROM PARICIPANTS:

For all participants, sincerity in answers to questions asked would be required. For participants who will be revisited, breakfast will not be taken till after necessary tests and others may be required to take glucose for confirmatory tests.

ETHICAL CONSIDERATIONS

The participation in this study will be purely voluntary and confidentiality of data and anonymity of the participants will be maintained throughout the course of this study.

RISKS TO SAFETY /BENEFITS OF INTERVENTION GROUP PATIENTS:

This study has no risk to participants. Ethical approval had been obtained from the Ethical Committee of Faculty of Pharmaceutical Sciences to further protect the patients. Confidentiality of data and anonymity of the patients will be maintained throughout the course of this study. Any act that will predispose the participant to harm will be avoided.

The under listed potential benefits are derivable from this study.

1. Knowledge of status of diabetes and hypertension.
2. Teachings on Diabetes, its risk factors and medication education.
3. Self-monitoring of blood glucose (SMBG) education and training.
4. Medication adherence counselling.
5. Lifestyle modification advice (to be aided with educational booklets).

COST IMPLICATIONS:

Eligible participants would be examined at **no cost (free of charge!)** by the Research Pharmacist.

CONCLUSION: Some participants may be required to submit their phone numbers with the research pharmacist for pre-information on the next visit. Eligible participants can also contact the research pharmacist for more personal details.

FEED BACK

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Appendix 2: Consent form

I have read and understood the terms and conditions that apply to this study, I willingly give my consent to participate in the study.

Identification number of participant_____

Signature ---------- Date ----------Phone number _____

Name of the researcher _____

Signature ---------- Date ---------- Phone number _____

Appendix 3: Data collection form

TOPIC: "PREVALENCE OF TYPE 2 DIABETES MELLITUS IN A UNIVERSITY COMMUNITY STAFF QUATERS" IN NIGERIA.

Kindly respond to the following items as the answers will be used only for this study and be handled with high degree of confidentiality

SECTION A: DEMOGRAPHIC DATA

Household's identification number _____ RESPONDENT'S Identification _____

1.	**Gender:** M [ ] F[ ]
2.	**Age:** 18-40[ ] 41-50[ ] 51-60[ ] Greater than 60[ ]
3.	**Marital status**: married[ ] single[ ] widowed[ ] divorced[ ]
4.	**Occupation:** civil servant [ ] self- employed/business[ ] student[ ] retired[ ]
5.	**Educational status:** No formal education [ ] primary [ ] secondary[ ] tertiary[ ]
6	**Staff Category:** Senior [ ] Junior [ ] Academic [ ] Non academic [ ]

SECTION B: ASSESSMENT OF RISK FACTORS

1.	Do you believe that diabetes mellitus has no cure? Yes [ ] No [ ]
2.	Have you ever gone for diabetes screening before now? Yes [ ] No [ ]
3.	Do you think maintaining a healthy weight is necessary in diabetes mellitus? Yes[ ] No[ ]
.	Have you ever been advised by any health professional to lose weight?Yes [ ] No [ ]
5.	Waist girth: less than 31 inches [ ] 31-35 inches[ ] greater than 35 inches[ ]

6. Has any of the members of your immediate family or other relatives been diagnosed with diabetes? One of your parents [ ] both parents [ ] none [ ]
7. Do you consume alcoholic drinks? Current- drinker [ ] ex-drinker[ ] never drinker[ ]
8. On the average, how many bottles of alcohol do you take in a week? less than7bottles [ ]
   7-12 bottles [ ] 12-24 bottles [ ] greater than 24 bottles [ ]
9. Do you smoke? Current smoker [ ] ex-smoker [ ] never smoker[ ]
10. How often do you take part in exercise? Everyday [ ] (**regular*) less than 3days in a week [ ] (**moderate*) Once in a while[ ] (**mild)* Not at all [ ] (**sedentary/no exercise*)
11. Which of these sets of food do you like to eat? Rice, garri, yam, akpu, bread [ ] Beans, plantain, soy beans [ ] Egg, butter, margarine [ ] Meat, fish, chicken, pork [ ] Fruits, vegetables, berries [ ]
12. How often do you consciously eat fruits and vegetables (not as an admixture to food)? Everyday [ ] Once in a while [ ] not at all [ ]
13. How would you describe your general health status?
    Excellent [ ] Very good [ ] Good [ ] Fair [ ] Poor [ ] Very poor [ ]

Laboratory values

	Laboratory values					
Paramenters	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit
Weight						
Height						
BMI						
SBP						
DBP						
RBS						
FBS						
OGTT						

2HPP						

Impression:

Normal [ ] Diabetic [ ] Pre-diabetes (IFG) [ ] Pre-diabetes (IGT) [ ] e