POSTPRANDIAL GLUCOSE AS MARKER OF GLYCEMIC CONTROL IN TYPE 1 SUDANESE DIABETICS

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بسم الله الرحمن الرحيم

(اقرأ باسم ربك الذي خلق،* خلق الإنسان من علق *
اقرأ وربك الأكرم* الذي علم بالقلم* علم الإنسان ما لم يعلم)
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DEDICATION

To parents for so much
To my sisters, brother and friends for their concern and tender love
To Moneira, Salih and Wagie
To the soul of my teacher Babkir Gurashi
To the diabetics
I am greatly indebted to Professor El Daw, Professor of medicine, University of Khartoum for his fatherly supervision, continual support and guidance.

My gratitude to my friend Dr. Yosif who has helped a lot in conducting this study. My thanks extend to the laboratory team in Gaber Abuez.

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Would also like to thank my teachers throughout my study in the primary, secondary, high schools and in the faculty of Medicine University of Gezira. Deep thanks to all citizens of my village, family and friends and their families for their trust, patients and encouragement. Special thanks and appreciation to my teachers in faculty of medicine U of K and Khartoum teaching hospitals for their valuable advices and supervision throughout my training programme. And finally thanks go to Moez for preparing the manuscript and to many whom couldn't be nominated.
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<th>Abbreviation</th>
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<tr>
<td>FBG</td>
<td>fasting blood glucose</td>
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<tr>
<td>2HPBG</td>
<td>2hour post breakfast blood glucose</td>
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<td>3HPBG</td>
<td>3hour post breakfast blood glucose</td>
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<tr>
<td>HbA1c</td>
<td>glycated haemoglobin A1c</td>
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<tr>
<td>NEFA</td>
<td>Non esterified fatty acid</td>
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<tr>
<td>MODY</td>
<td>Maturity onset diabetes of the young</td>
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<td>GLUT</td>
<td>Glucose uptake transporter</td>
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<tr>
<td>SGLT</td>
<td>Sodium sensitive Glucose transporter</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>UAER</td>
<td>Urinary albumin excretion rate</td>
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<td>GAD</td>
<td>Glutamic acid decarboxylase</td>
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<td>ICA</td>
<td>Islet cell antibodies</td>
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<td>IFG</td>
<td>Impaired fasting glucose</td>
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<td>Impaired glucose tolerance</td>
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<td>IAPP</td>
<td>islet amyloid polypeptide</td>
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<td>WHR</td>
<td>Waist hip ratio</td>
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<td>FFA</td>
<td>Free fatty acid</td>
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<td>AACE</td>
<td>American association of clinical endocrinologist</td>
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<td>SU</td>
<td>Sulfonylurea</td>
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<td>SUR</td>
<td>Sulfonylurea receptor</td>
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<td>TZDS</td>
<td>Thiazolidinediones</td>
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<td>PPAR</td>
<td>Perioxisome proliferative activator receptor</td>
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<tr>
<td>NPH</td>
<td>Insulin Protamine Hagedorn</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>Abbreviation</td>
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<tr>
<td>ESRD</td>
<td>End Stage Renal Disease</td>
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<td>The A1C</td>
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<td>SMBG</td>
<td>Self monitoring of blood glucose</td>
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<td>glycated serum protein</td>
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<td>glycated serum albumin</td>
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<td>HPLC:</td>
<td>High performance liquid Chromatography</td>
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<td>AdA:</td>
<td>adenosine deaminase assay</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Study prospective Diabetes</td>
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<tr>
<td>ICI</td>
<td>Institute of continuous improvement</td>
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<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
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<td>ADA</td>
<td>American of drug Association</td>
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<tr>
<td>FDA</td>
<td>Federal Drug Association</td>
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<tr>
<td>ACE-I</td>
<td>Angiotensin converting enzyme inhibitors</td>
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<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td>HOT</td>
<td>Hypertension Optimal Treatment</td>
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<td>HOPE</td>
<td>Hypertension optimal Practice Evaluation</td>
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<tr>
<td>Steno-2</td>
<td>Scandanavian Trial intensive Treatmentl of diabetes is needed to be optimized</td>
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OBJECTIVE: To compare the accuracy of fasting blood glucose, two hour post breakfast glucose and three hour post breakfast glucose (FBG, 2hPBG, 3hPBG) in inferring glycemic control as judged by glycated hemoglobin (HbA1c); and to evaluate their association with diabetic complication. DESIGN: Description of type 2 diabetes glucose profile and Comparative cross sectional Study. SETTING: Sudanese population. Patients: 99 People aged 30-70, 55% females, with type 2 diabetes on oral therapy. FBG, 2hPBG, 3hPBG were measured three times one-week apart; by the end of the month HbA1c was measured. Patients were evaluated for clinical evidence of complications; haemoglobin, serum creatinine and ECG were done. MAIN OUTCOME MEASURES: Sensitivity, specificity, positive and predictive values. RESULTS: Patients control profile was poor in the majority. Correlations among different parameters showed FBG to be strongly correlated with HbA1c (r=0.601; P=0.000). 2hPBG correlated weakly if at all with HbA1c(r=0.202; p=0.102) but has good prediction of poor control (p = 0.000). 3hPBG correlation with HbA1c(r=0.547; p=0.000) was less. 2hPBG, 3hPBG correlated very well both on single determination and means of values(r=0.912, 0.900.P=0.000).Correlations with FBG were less r=0.830, 0.841 respectively. Poor correlation was shown between level of glycemia and long term diabetic complications except erectile dysfunction (P=0.35). Conclusion: Sudanese diabetic should have their postprandial glucose measured, in addition to fasting glucose and /or HbA1c. 2 and 3 hour postbreakfast blood glucose can be used alternatively. Medications specifically designed at the management of postprandial hyperglycemia should be included in the routine treatment of Sudanese diabetics.
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INTRODUCTION

Diabetes is a global epidemic that affects more than 150 millions worldwide. Its overall prevalence is 2-4%. Being low 1-3% in the third world, affects 10-20% of adults in many developed countries and as high as 30% in Pima Indians population. The WHO stated in 1998 that a 122% rise in the number of adults with diabetes is projected by 2010 to reach 300 million adults worldwide. Arabs with their common genetic background make the thrifty phenotype hypothesis an attractive proposition to explain the explosive emergence of diabetes in the Arabs' region. This is closely related to obesity, ageing and growth of population, unhealthy diet and sedentary lifestyle.

U.K. Prospective Diabetes Study and other clinical trials had clearly demonstrated the benefit of good glycemic control in markedly reducing long term complications. Measurements of glycemic control had witnessed major changes over the years; glycated HbA1c provides an objective measure that predicts development of complications. Accumulating evidence had suggested postprandial glucose as better tool.

Diabetes exerts a huge toll in illness, death, loss of quality of life and economic consequences at societal and individual levels. Many challenges lie ahead, diabetes must be diagnosed earlier and complications must be prevented or treated. New and existing medicine and technologies must be used in innovative ways.
**Definition:**

Diabetes Mellitus is a chronic heterogeneous group of metabolic disorders characterized by hyperglycemia due to deficiency or decrease in action of insulin or both and increased glucose production.\(^6\)\(^7\) It is often associated with metabolic dysregulation causing changes in multiple organs that imposes tremendous burden on patients with diabetes.\(^8\)

**Historical Background**

Diabetes was described for the first time by ancient Egyptians 3500 years ago. The term “diabetes” was put by Aretaeus (81-133 AD), he said “Diabetes is a melting down of the flesh and limbs into urine, the patients never stop making water but the flow is incessant as if from the opening of the aqueducts”.\(^9\) Later the word mellitus (Honey sweet) was added by Thomas Willis 1675.

In 1776 Dobson confirmed the presence of excess sugar in urine and blood as cause of their sweetness. Claude Bernard in 1857 introduced the concept of excess glucose production in diabetes. Messing in1889 described the role of glucose production as a cause of diabetes. Insulin was prepared by Bantiry and Best in 1921, oral medicine waited till 1955 to be marketed, first was tolbutamide.\(^10\) Thereafter greater insight and discoveries were made.

**EPIDEMIOLOGY**

Diabetes represents the ninth leading cause of hospital admission in Sudan 1.9 %. The number of patients had almost doubled in 2000 compared to 1997 (6863 vs. 3619).\(^11\)
The crude prevalence of diabetes in Sudan was found to be 3.4% (men 3.5%, women 3.4%). Impaired glucose tolerance was estimated at 2.9%. The highest crude prevalence was seen in the northern part (5.5%) and the lowest in the western desert-like parts (1.9%). The highest prevalence was seen in Danagla tribe (8.3%). Family history of diabetes and obesity were associated with higher rates. The average hospital death attributed to diabetes over the past four years (1997-2000) was 5.89%.

Traditionally thought to affect individuals older than 40, however type 2 diabetes is being recognized increasingly in younger age groups largely associated with obesity. It comprised some 30% of new cases of diabetes in second decade of life in native Americans. In China and Japan and Pacific Islands more than 70% of diabetic children have type 2 diabetes. Type 2 diabetes in Japanese schoolchildren has increased more than 30 folds over the past 20 years.

Incidence increases with age, 10% of North European aging more than 70 years have diabetes. The reported crude prevalence of type 2 diabetes in Kuwait in 1996 was 7.6%. It was 15% and 26% for age groups 40-50 and 76 respectively. Diabetes is slightly more common in females (1: 0.97). 50% of cases remain undetected. African & Hispanic-Americans, Asian, Pacific Islander are highly susceptible. Arabs are prone to high rates of diabetes; in 1997 Tunisia reported (7-13%), Kuwait (7.6%), Bahrainian age standardized prevalence were 25%, 48%, 23% in Jaafari, Sunni and Iranian Arab respectively. In the Sudan the crude prevalence fell from 5.5% in Arab predominant region to 1.9% in African predominant desert-west part.

Classification of Diabetes (Aetiology)
The 1979 classification has been replaced by 1998 with many modifications. It reads:-

1. **Type 1 diabetes:**
Specified destruction of pancreatic $\beta$ cells usually with complete insulin deficiency: immune mediated or idiopathic.

2. **Type 2 diabetes:** *
Predominantly insulin resistance coupled with a relative insulin deficiency or mainly insulin excretion defect associated with insulin resistance.

3. **Other specific types:**
1. Genetic pancreatic cell dysfunction.
   *MODY1-3 (maturity onset diabetes of the young)
2. Mitochondrial DNA defect diabetes
3. Others:
   A. Genetic insulin action defect: Insulin resistance type, Leprechaunism, Rabson Mendehall syndrome, lipoatrophic diabetes etc.
   B. Exocrine pancreas diseases:
      Pancreatitis, Cystic Fibrosis, Fibrocalculous pancreas, Haemochromatosis, neoplasia and trauma/pancreatectomy
   C. Endocrinopathy: Acromegaly, Cushing syndrome, Phaeochromocytoma, Hyperthyroidism, Glauconagonoma, Somatostainoma, Aldosteronoma etc
   D. Drug induced:
      Corticosteroids, thiazides, beta adrenergic antagonists etc
   E. Infections: cytomegalovirus, roseola infantum etc
   F. Unusual forms of immune mediated diabetes:
      “Stiff-man” syndrome, anti insulin receptor antibodies.
   G. Other genetic syndromes associated with diabetes:
      Down, Klinefelter, Turner syndromes, Wolfram syndrome, Friedrick’s ataxia, Huntington’s chorea, Laurence-Moon–Biedl syndrome, Myotonic dystrophy, Porphyria, Prader –Willi syndrome, and others.
4. Gestational diabetes mellitus (GDM) *

*Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

*Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., "honeymoon" remission).
Blood glucose levels are precisely regulated in health and rarely stray outside the range of 3.5 – 7.0 mmol/l (63-126 mg/dl) despite the varying demands of food, fasting and exercise. After eating plasma glucose concentrations rise to a peak in 30-60 minutes and return to basal concentrations or below within 2-3 hours. Principal organ of glucose homeostasis is the liver, which stores glucose in the fed state as glycogen and releases it in non-fed times to match the rate of glucose utilization by peripheral tissues. The liver produces 90% from the 200 g of glucose produced and utilized each day.

Glucose utilization:
The brain needs glucose as fuel. Other tissues like muscles or fat use glucose electively. The effect of insulin peaks associated with meals is to lower the threshold for glucose entry into cells. At other times energy requirements are largely met by fatty-acid oxidation. There are many glucose transporters to facilitate glucose diffusion like sodium sensitive SGLT 1,2,3 and GLUT 1,2,3,4,5. GLUT4 which is found in muscles & adipose tissues is insulin sensitive. In the fed state glucose is taken by muscles, liver and adipocytes and stored as glycogen and triglyceride.

Insulin:
Is a 51 polypeptide hormone secreted by the beta cells (IC) from the pancreas as proinsulin which is cleaved to insulin and c-peptide. It is the major regulator of intermediary metabolism of carbohydrate, protein synthesis and lipogenesis.
It facilitates the diffusion of glucose into cells and regulates membrane polarization and ion transport by regulating Na-K\(^+\)ATPase. Insulin is secreted in a pulsatile pattern with small secretary bursts occurring every 10 minutes superimposed upon greater amplitude oscillations every 80-150 minutes.\(^7,19,20\)

Meals and other main stimulants induce large -4-5 folds- bursts (vs. basal) of insulin that usually last for 2-3 hours before returning to baseline.\(^7,19\) Once secreted in the portal vein, 50% would be extracted and degraded by the liver , the unextracted re-enters the circulation. Elimination half life is 1.6-3.4 minutes (5.3-7.8 minutes in diabetics).\(^20\)

Insulin is rapidly metabolized in the liver, kidney (80%) and muscles by glutathione transhydrogenase. Metabolites appear in the urine.\(^19,20\) Counter regulatory hormones e.g. glucagon, growth hormone and adrenaline shift the insulin dose-response curve to the right resulting in greater production and less utilization of glucose for a given level of insulin.\(^19,21\)

**Insulin receptor (IR):**

Is a glycoprotein coded for by the short arm of chromosome 19. It is a dimer with two alpha subunits which include the binding sites for insulin, and two β subunits which traverse the cell membrane. Binding of insulin activates tyrosine kinase initiating the metabolic cascade response.

Consequently the GLUT4 glucose transporter migrates to the cell membrane. The insulin–receptor complex is then internalized, insulin is degraded by insulin protease, and the receptor re-circulates to the cell surface.\(^7,8,19\)

Insulin receptors are widely distributed even in insulin independent human brain cells with no difference in affinity to both human and porcine insulin.\(^23\)
Pathophysiology and risk factors of type 2 diabetes

Hyperglycemia is produced by the interplay of relative lack of endogenous insulin, insulin resistance and increased production of glucose.\textsuperscript{7,8,24} This results in decreased glucose transport in muscles, elevated hepatic glucose productions and increased fat breakdown.\textsuperscript{7,24}

The genetics of diabetes type 2 is complex and not fully understood but it is polygenic and heterogeneous. Monozygotic twins Concordance is about 100\%.\textsuperscript{25} Siblings of patients with type 2 diabetes have a lifetime risk of almost 40\%.\textsuperscript{8} 25\% of patients have first degree relative with type 2 diabetes.\textsuperscript{26} Evidence had supported the theory of inherited components for both pancreatic $\beta$ cell failure and insulin resistance.\textsuperscript{24,25}

Despite extensive studies few genes were identified accounting for a few number of cases. Increased expression of genes coding for glucose-6-phosphatase and 12-lipoxygenase were demonstrated.\textsuperscript{26} Recent evidence had implicated overexpression of glucose-6-phosphatase gene in the beta-cell dysfunction that occurs in ob/ob mice.\textsuperscript{26} Other genes involved those coding for insulin receptor (AD), glucagon receptor, Esokinase.\textsuperscript{7,24,25}

Monogenic diabetes accounts for less than 5\%.\textsuperscript{7,25} Best studied is Maturity Onset Diabetes of the Young (MODY) which is autosomal and dominantly inherited (AD). It results from mutations in at least three different genes on chromosomes 20 (\textit{MODY 1}), 7 (\textit{MODY 2}–glucokinase\textsuperscript{5}), and 12 (\textit{MODY 3}).\textsuperscript{25,26} Monogenic diabetes also includes the maternally inherited diabetes shown to be associated with mitochondrial DNA mutation A to G 3243. It accounts for 1\% of diabetes, associated with deafness and myopathy.\textsuperscript{27}
**Insulin resistance:**

Patients with type 2 diabetes retain 50% of β cell mass at autopsy.\(^8\) In established type 2 diabetes insulin mediated suppression of hepatic glucose production and tissue glucose uptake are impaired. Glucose clamp studies in patients with type 2 diabetes showed a defect in insulin action post insulin membrane receptor.\(^7,28\) Defects in intracellular oxidation and storage of glucose (as glycogen) have been identified.\(^28\) Groop et al showed that insulin resistance is confined to those with microalbuminuria and hypertension.\(^29\) In non-obese blacks with type 2 diabetes both insulin resistant and sensitive subtypes of diabetes have been identified. Abdominal fat deposits correlated with the resistant group.\(^30\) Recent evidence suggested elevated free fatty acids (NEFA) as a driving force behind insulin resistance and even β cell dysfunction.\(^24,31\)

**Lipotoxicity & Glucotoxicity:**

Increased circulating free fatty acids or increased cellular fat content have diabetogenic effect, reduction greatly improved glycemia.\(^32\) Increased levels of plasma glucose lead to altered level of intracellular glucose. Progressive hyperglycemia was associated with worsening of overall metabolic condition.\(^32\) Hawkins et al showed the contribution of hyperglycemia and/or hyperlipidemia to the impaired effectiveness in regulating glucose fluxes in type 2 diabetes. Short term normalization of glucose might break the vicious cycle.\(^33\)

**Environmental factors:**

In Utero Environment Effects:
Many studies showed that persons with low weights at birth or at one year had higher rates of type 2 diabetes later in life. This fetal origin hypothesis showed that diabetes and stroke, coronary heart disease, hypertension were results of adaptations made by the fetus in response to malnutrition in utero.\textsuperscript{34,35} Insulin resistance may explain the risk for these disorders.\textsuperscript{35} However Stanner SA, Bulmer K and associates demonstrated that intrauterine malnutrition wasn't associated with glucose intolerance in adulthood but with endothelial dysfunction and stronger influence of obesity on blood pressure.\textsuperscript{36} Sobngwi E et al showed the increased occurrence of impaired glucose tolerance and defective insulin secretion in adults who had been exposed to diabetic environment in utero.\textsuperscript{37}

**Thrifty phenotype hypothesis:**

Poor nutrition in fetal and infant life is detrimental to the development and function of beta cells and insulin sensitive tissues, leading to insulin resistance under the stress of obesity. It proposes that defective insulin action in utero results in decreased fetal growth as conservation mechanism, but at the cost of development of obesity–induced diabetes in later childhood and adulthood.\textsuperscript{5,7,24,35}

**Obesity:**

Obesity is present in 80% of patients with type 2 diabetes.\textsuperscript{8} It is associated with acquired insulin resistance. Compensatory hyperinsulinemia in obese patients' down regulates membrane insulin receptors but the maximal response to insulin is preserved.\textsuperscript{28}
Upper body (android) obesity particularly visceral fat deposition (indicated by high waist: hip ratio WHR=0.9) is more closely associated with glucose intolerance and other features of insulin resistance syndrome than the lower body (gynaecoid WHR=0.7) obesity.  

Calculations suggested that subjects who are 50% overweight have 12 folds increased risk for diabetes. Populations with high prevalence of type 2 diabetes like Pima Indians, Mexican American, South Asians are predisposed to abdominal obesity. Acausal relation between leptin coded for by ob gene, and insulin sensitivity has been suggested.

**Smoking and alcohol:**

Current smoking (25 or more cigarettes daily) doubles the risk of diabetes among a healthy men population whereas moderate alcohol consumption significantly decreases the risk of diabetes.

**Inflammatory markers:**

Maria Anes showed that inflammatory markers; raised white cell count, sialic acid and orosomucoid were associated with the development of diabetes in middle-aged adults. They probably reflect the pathogenesis of type 2 diabetes.

**Islet amyloidosis:**

Islet amyloidal deposits are derived from islet amyloid polypeptide (IAPP) which is co-secreted with insulin. They were seen in more than 90% of diabetics, greatest in those who require insulin. It has been implicated in beta cell cytotoxicity (reduction in cell mass) and interference with glucose and hormone transport.
Proposed mechanisms are extracellular and intracellular deposition, increased expression of apoptosis related genes e.g. p53, p21; and oxidative stress. Its potential therapeutic targets include medications to inhibit IAPP production and to prevent fibril deposition.\textsuperscript{43}

In conclusion type 2 diabetes occurs when a diabetogenic environmental event like westernized lifestyle mainly physical inactivity, overweight, high energy yielding dietary habit and obesity superimpose upon genetically programmed defect of beta cell failure and insulin resistance.

**Clinical Presentation**

Type 2 diabetes represents 90\% of the diabetics; it is 10 times more common than type 1.\textsuperscript{24}

The diagnosis of diabetes is readily entertained when classic symptoms are present: polyuria, polydipsia (excessive thirst), weight loss and lack of energy. Other symptoms that may suggest hyperglycemia include blurred vision and lower extremity paraesthesia.\textsuperscript{7,8,24}

In many cases complications are the presenting features. They include infections like recurrent boils and tuberculosis\textsuperscript{16,44}, hyperglycemia as diabetic ketoacidosis or hyperosmolar non-ketotic coma.\textsuperscript{8,16,17,44} Long term complications include: microvascular: diabetic retinopathy, neuropathy and nephropathy. Macrovascular diseases (CVD) which include: Coronary heart disease, Carotid and peripheral ischaemia leading to myocardial ischaemia (CHD), TIA/stroke and limb amputation.
High blood pressure is common (40%)\textsuperscript{17,18,44} and should warrant screening.\textsuperscript{16} Most patients are however asymptomatic for a decade and could only be detected on routine screening of urine or blood.\textsuperscript{7,8,16,24,45}

**Physical Examination:**

Should emphasize on measuring the weight, height and blood pressure. Careful cardiovascular, neurological examination including fundi, foot and peripheral pulses and skin examination for evidence of complications.\textsuperscript{7,8,16,24,45}

**The dysmetabolic syndrome:**

Previously known as Syndrome X.\textsuperscript{46} It is an often finding in type 2 diabetes and is due to insulin resistance.\textsuperscript{47} Diabetes is only the tip of the iceberg.

**Criteria for diagnosis:** Any three of the following\textsuperscript{7,24,46,47}:

- Abdominal obesity: Waist to hip ratio (WHR) >1.0 in Females, > 0.8 in Males.
- Lipid disorders: Triglycerides (TG) >150,
  high density lipoprotein (HDL)< 40 mg/dl
- Blood pressure: >180/85mmHg.
- Fasting blood glucose: >110mg/dl

**Diabetic Complications**

UKPDS had shown that 50% of patients with type 2 diabetes had already one or more complications by the time of diagnosis.\textsuperscript{48} Diagnosis of diabetes immediately increases the risk of developing various clinical complications that are largely irreversible and result from both macrovascular and microvascular derangements.\textsuperscript{8,16,38,49}

Diabetes is progressive. When followed over 6 years up to 18% had developed one or more diabetes clinical end point.\textsuperscript{50}
Diabetic complications can be divided into:

1. Acute complications.
2. Long term complications.

**Acute complications:**

1/ Diabetes keto acidosis (DKA):

DKA results from absolute insulin deficiency or insulin inefficacy with elevated levels of counter regulatory hormones. 

Although classically associated with type 1, a high proportion (39%) of DKA in non-white adults occurs in persons with type 2 diabetes especially in those with previously undiagnosed. 51 58% of DKA presenting to Khartoum (1997-1998) were type 2. Poor compliance precipitated half of cases. 52

When treating patients with hyperglycemia, it is important to consider the possibilities of both acidosis and hyperosmolarity, no matter what the age or presumed type of diabetes. 53

2/ Hypoglycemia:

Low blood sugar is a common problem in diabetics. It is crucial to consider hypoglycemia in all patients with neurological symptoms because outcome depends on its duration. A recent study of hospitalized patients revealed an overt incidence of hypoglycemia of 1.2%; of these 45% were diabetics. 53 Type 2 patients have preserved warning of hypoglycemia till late in life. 24

3/ Hyperosmolar non–ketotic coma (HONK):

It is a non acidotic state of a generally more marked hyperglycemia with significantly increased plasma osmolarity. 7,8,38

4/ Lactic Acidosis:
A rarity that occurs in the setting of collapse or severe infection, renal, hepatic decompensation or hypoxia particularly when the patient is on metformin. \(^{38}\)

**Long term complications:**

**Cardiovascular complications (CVD)**

The most costly complication of diabetes up to 80% of adult diabetic have clinical or subclinical coronary heart disease at any given point in time. \(^{45}\) 75-86% of all deaths in adults with type 2 diabetes are due to macrovascular events. \(^{45,54,55}\) The relative risk compared to non diabetic is 2-5 folds for CHD and myocardial infarction(MI), 2-3 for stroke and 40 folds for amputation.

Cardiovascular risk factors in diabetes are the same as in non-diabetic in addition to hyperglycemia, prothrombotic diabetic state and microalbuminuria. \(^{56}\) Also there is an increase in heart failure (diabetic cardiomyopathy) caused by ischaemia, high blood pressure and myocardial cell dysfunction due to chronic hyperglycemia. \(^{7,56}\)

**Diabetic eye**

Eye complications in diabetes include cataract, glaucoma and retinopathy, retinal vein thrombosis, optic atrophy. \(^{7,8,16,38}\) Diabetes is a leading cause of blindness in working age adults in US. National Eye Institute estimates that 90% of lost vision is preventable. \(^{57}\)
The relative risk of retinopathy compared to non diabetic is 20. Prevalence of retinopathy varies with race, age and duration of diabetes. Abnormalities start by changes in leukocytes adhesion and alteration in retinal blood flow. Microvascular defects: retinal hemorrhages, microaneurysm and intraretinal microvascular changes supervene. Progressive non-perfusion of retinal capillaries results in retinal ischemia and increase in growth factors leading to abnormal proliferation of new vessels.

These vessels are fragile, bleed easily and undergo scarring and fibrosis leading to traction on the retina, retinal detachment, and severe visual loss. At any stage retinal vessels may become abnormally permeable resulting in transudation of blood serum components into the retina and the macula (edema and exudates). Knock mice model study suggested that insulin signaling in vascular endothelial cells of the retina may play an important role in the progression of diabetic retinopathy and expression of angiogenic factors (insulin receptor role).

Hypertension is an independent risk factor for diabetic retinopathy.

**Diabetic nephropathy:**

Diabetes is the leading cause of End Stage Renal Disease (ESRD). In US about 28,000 patients with diabetes develop ESRD every year. Most future ESRD is probably preventable. Relative risk compared to non diabetic is 25. Genetic predisposition to hypertension and persistent elevation of GFR predicts an increased risk of nephropathy. The risk is 3-6 folds higher in African-American, Latinos and Native Americans.
Hyperglycemia in the diabetic range can cause microalbuminuria. Controlled trials demonstrated that intensive glucose lowering prevents the onset and progression of microalbuminuria with a continuous graded relationship between level of glycemia and risk of abnormal urinary albumin excretion (UAER). Mechanisms of glucose related albuminuria include glycation of basement membrane proteins with loss of charge selectivity and glomerular hyperperfusion and hyperfiltration. 11-67% of patients progress to overt proteinuria over 5-15 years of follow up. Progression to ESRD varies individually. Heterogeneity in progression of microalbuminuria is determined (in addition to variation in glycemia) by baseline UAER, cigarette smoking, levels of blood pressure, serum lipids and genetic effect, and diabetic retinopathy. Other factors which don't seem to act as risk factors include obesity, known duration of diabetes, arterial blood pressure, serum creatinine concentration and pre-existing coronary heart disease. Diabetes is the cause of kidney failure in 42% of patients on dialysis.
One common and early complication of diabetes. The commonest form is a diffuse progressive polyneuropathy affecting mainly the feet. It is predominantly sensory, often asymptomatic, and affects 40-50% of all patients with diabetes. Other forms include polyradiculopathy which presents with root pain and motor weakness. Lumbar plexus or femoral nerve affection causes pain and weakness in the hip and thigh (diabetic amyotrophy). Also occur are polycranioneuropathy and monocranioneuropathy commonly 3rd, 4th, 6th cranial nerves, mononeuritis multiplex and Bell's palsy. Autonomic neuropathy is common. It manifests as gastropathy, oesophageal dysfunction&cytopathy. Erectile dysfunction is a common early sign of neuropathy.

**Diabetic foot:**

Diabetes is the leading cause of non-traumatic lower extremity amputation in the US with 15-40 folds increase in risk compared to the nondiabetic population. Each year 67,000 limbs are lost secondary to diabetic vasculopathy and neuropathy. 15% of diabetics develop foot ulcer. Risk factors include duration more than 10 years, male gender, smoking, peripheral neuropathy, vasculopathy and poor glycaemia. Every 2% increase in HBA1c increases the risk of ulcer by 1.6% and leg amputation by 1.5 times.

**Mortality:**

Diabetes is the fourth leading cause of death in US. It doubles the annual mortality compared to non diabetic (5.4%). Life expectancy of a diabetic is decreased by 5-10 years.

**Laboratory evaluation:**

- Urine tests:
To evaluate for ketones, glucose. Double void technique ensues that the specimen being tested reflects the plasma of the time. The patient should empty the bladder, discard the specimen and a further one passed 10-15 minutes later is collected and tested. Urine collected 1-2 hours after meal will recognize more of milder cases than overnight fasting sample.

**Blood tests for glucose:**

Normal range (reference range): 19,38

- Fasting 3.5-5.5 mmol/L (74-106 mg/dl) 64
- Postprandial up to 8.7 mmol/L.

The biological variation is 7.9% and the critical difference is 24.5%. The absolute value of critical difference at upper reference limit is 26 mg/dl. Glucose homeostasis varies with age, sex, time of the day and menstrual cycle. 64,66 Fasting blood glucose increases 2 mg/dl per decade after the age 30, 1 hour postprandial increases by 10 mg/dl and 2 hours postprandial by up to 100 mg/dl plus age in years after the age of 40. 65

Plasma glucose is determined in a grey top (Sodium fluoride) tube which inhibits red cells metabolism. 24 Serum glucose measurements give 15% lower results than plasma. 24,66

**Definition of Diabetes:** 24,38,45,66

Normal fasting plasma sugar (FPS) less than 110 mg/dl (6.1 mmol/l)
Impaired fasting glucose (IFG): Fasting plasma glucose greater than 110mg/dl and less than 126mg/dl.

Impaired glucose tolerance (IGT): 2-hour plasma glucose greater than or equal to 140mg/dl and less than 200mg/dl.

**Diagnostic Criteria of Diabetes mellitus:** 7,8,16,18,38

- Classic symptoms of diabetes plus casual blood glucose greater than 200 mg/dl (11 mmol/L) measured at any time without attention to food.
- Fasting blood glucose greater than 126 mg/dl (7.0 mmol/L), no food (caloric) intake for more than 8 hours.
- Blood glucose 2 hours after oral glucose loading done with 75g of glucose in water, greater than 200 mg/dl (11 mmol/l).

In the absence of unequivocal hyperglycemia associated with acute metabolic decompensations, the results should be confirmed by repeat testing on a different day with any of the three methods.

**Oral glucose tolerance test (OGT):** 16,66 Conventional OGT should no longer be used except for borderline cases or diagnosis of gestational diabetes.

**Other laboratory tests** include: urine for microalbuminuria (2 out of 3 tests >300mg/24hours) or proteinuria and Cultures. Serum creatinine, lipid profile, HbA1c, insulin and C peptide levels. Auto antibodies (ICA, GAD65, tyrosine-phosphatase-like auto antigen IA). 7,8,24,38

**Differentiation between type 1 and type 2 diabetes:**
Type 2 diabetes can be differentiated from type 1 by the presence of ethnicity, family or gestational history of diabetes, obesity and acanthosis negricans.\textsuperscript{24,67} Greater than 10\% improvement in glucose levels in response to oral drugs plus the occurrence of characteristic diabetes dyslipidemia (high TG) would further aid in the diagnosis. Usually there is no need for measuring C peptide, auto antibodies GAD65, ICA.\textsuperscript{7,24,67} However the gold standard tool is “glucose clamp” procedure which is used only in research settings.\textsuperscript{28} Clinicians can make an educated clue to which type of diabetes clinically and by using simple tests.\textsuperscript{67}

**Screening:**

Should be offered to the high risk groups. They entail those who have first degree relative with type 2 diabetes, females with a history of big babies (4kg), gestational diabetes or polycystic ovary syndrome. And hypertensive individuals plus those with high lipids.\textsuperscript{18, 24,38,45} Screening by blood glucose measurements perform more favorably than urinary glucose or HbA1c, and measuring postprandial glucose levels may have advantages over fasting levels.\textsuperscript{24,45,68}

The optimal interval for screening is unknown, even though periodic, targeted, and opportunistic screening within the existing health care system seems to offer the greatest yield and likelihood of appropriate follow-up and treatment.\textsuperscript{68}

**Management**
The direct and indirect cost of managing diabetes in US is 105 billions annually, majority spent on hospital care.\textsuperscript{69} The American Association of Clinical Endocrinologists (AACE) published a system of intensive self management of diabetes. It entails three phases: Initially a customized-therapeutic approach, then the follow up phase. Thence ongoing assessment of complications, re-education of patient and encouragement to maintain enthusiasm for the difficult task of intensively managing blood glucose.\textsuperscript{70}

Special talents of diabetes education, nutritionist or hospital diabetes center would be helpful. Educational handouts, appropriate web site references should be provided. Patients should be encouraged to purchase home glucose monitor.\textsuperscript{45,69,70}

**Diet and Exercise**

It does work initially but as time goes on, patients start to sneak back into their customary diet.\textsuperscript{71} Best regimen is a relatively high fibre, high carbohydrate, low fat and low protein, with plenty of vegetables.\textsuperscript{72}

**Medications:**

Physician should not wait for the effect of exercise and diet as there is no mild or severe diabetes, all patient should be offered best of care available.\textsuperscript{7,8,16,24,38,45}

**Sulfonylurea (SU)**

Derivatives of sulfonamide rediscovered by Frank 1952.\textsuperscript{73} The most experienced oral hypoglycemic drug.\textsuperscript{74} They directly stimulate insulin release by binding to a receptor (SUR) on the $K^+$-ATP channel in the $\beta$ cell membrane. This closes the channel causing depolarization and insulin release.\textsuperscript{74,75}
Members of this class have similar efficacy but different pharmacokinetics. They were introduced in generations; the 1st are Acetohexamide, tolbutamide & glibenclamide. The 2nd are Gliclazide, glyburide, Glipizide.

Prevalence of primary failure may be as low as 15% but secondary failure occurs in 7-10% of patients every year as β cell function declines. Most patients require additional medication after about five years. Few side effects are seen other than hypoglycemia which occurs more with glyburide commonly in renal failure & hepatic diseases. Despite earlier concerns UKPDS proved that SU didn't increase CVD events.

**Biguanides:**

The active ingredient in Galega officinalis (Goat’s rue) herb, guanidine had been used to synthesize metformin in 1950’s. Metformin is the only available drug. It reduces gluconeogenesis and glycogenolysis by acting primarily on the liver, adipocytes and myocytes. It increases insulin-stimulated glucose uptake by 10-40%. Efficacy is similar to SU with no weight gain. It significantly reduces TG, LDL and increases HDL. The main side effects are metallic taste, GI upset. Lactic acidosis is rare (3/100,000 per year). It mainly occurs in renal impairment, hypoxia, severe heart failure and decompensated liver states. UKPDS suggested a preferential benefit against macrovascular events in obese. It is the ideal choice for obese diabetic.

**Thiazolidinediones (TZD):**

Available are Pigolitazone & rosiglitazone. The drug interacts with the nuclear
peroxisome proliferative activator receptor (PPAR) forming a complex that regulates genes involved in lipid metabolism in fat and muscles. This leads to reduction of release of NEFA from adipocytes with reduction in insulin resistance & hepatic glucose output.\textsuperscript{74-76} They positively affect lipids, high blood pressure, reduce vascular inflammation and vascular smooth muscle proliferation.\textsuperscript{69,74,76} The main side effects are oedema, weight gain and exacerbation of heart failure. Liver toxicity is rare than with troglitazone.\textsuperscript{45,69,73-74}

**Alpha glucosidase inhibitors:**
Available are acarbose, miglitol. They reduce and delay carbohydrate absorption by competitively inhibiting disaccharidases in the intestinal brush border and pancreatic alpha amylase. They are used in obese with poor diabetes control. GI upset limited their uses.\textsuperscript{69,74,75-76}

**Insulinotropic short acting secretagogues(Non SU)**
Meglitinide analogues like repaglinide, nateglinide, and mitiglinide
They have similar action to SU but more potent, rapid onset and shorter duration of action and less hypoglycemia.\textsuperscript{78} Allow premeal dosing and better control of postprandial glucose excursion.\textsuperscript{24,69,74,76,78}

**Insulin:**
Insulin is the last resort for type 2 diabetes.\textsuperscript{79} Recombinantly produced. It is indicated in severe diabetic complications, severe infections, in major surgery and at gestation, as bridge to treat glucotoxicity.\textsuperscript{20,69,76} Insulin types are Rapid acting, basal insulin intermediate (NPH:Neutral Protamine Hagedorn,
INS: insulin zinc suspension) and premixtures. Side effects include hypoglycemia, skin allergy, lipoatrophy-hypertrophy & insulin resistance.

Insulin analogues: are chemically modified insulins; Ultra-rapid are insulin lispro, Aspart. They are more rapidly absorbed from subcutaneous tissues (5 minutes) and remain active for shorter duration than soluble human insulin. Longer acting insulin glargine (di-arginyl insulin analogue, Lantus) which remains essentially unchanged for 24 hours, and is unaffected by the site of injection.

**Future Therapy:**

Imidazole derivatives S-21663: glucose independent secretagogue.

Morpholinoguanidine BTS 67582: stimulates insulin secretion in site separate form SUR.

Non-TZD insulin sensitizers: G1262570X (GG570) and D chiroinositol.

GLP-1 (7-36 amide): a natural enteric incretin hormone that improves pancreatic beta-cell and alpha-cell sensitivity to glucose.

Organic vanadium compounds: enhance insulin biosynthesis and secretion.

**Modern methods for insulin delivery:**

Innovative ways for insulin administrations include:

Inhaled Insulins which have excellent control, safety and patient acceptance. It will be stable at room temperature for up to 2 years. Systems available are inhaled therapeutic system and hand hold inhalation device.

Oral insulin preparations are already being used in phase 3 clinical trials with reports of good effectiveness and accurate dose titration.

Infusion insulin pumps provide near physiological control of glucose.
**Rational drug approach to type 2 diabetes:**

The first modality is lifestyle adjustments aimed at improving endogenous insulin sensitivity or insulin effect. This can be achieved by increased physical activity and bodyweight reduction with diet and behavioural modification, and the use of pharmacological agents or surgery.\(^{24,45,69,82}\) Secondly is to increase availability of insulin by giving exogenous insulin, insulin analogues, sulfonylurea and insulin secretagogues (repaglinide). The association between hyperinsulinaemia and premature atherosclerosis is still a debatable question.\(^{82,83}\) The third modality consists of agents such as biguanides and glitazones which enhance insulin sensitivity, or agents that decrease insulin requirements like the alpha-glucosidase inhibitors. Therapy should be individualized based on the degree of hyperglycemia, hyperinsulinaemia or insulin deficiency. Efficacy, safety, affordability and ease of administration should all be considered.\(^{82}\)
HYPERGLYCEMIA

The diabetes control & complications trial (DCCT)\textsuperscript{84} conclusively proved that better glycemic control mitigates the ravages of microvascular diabetic complications in type 1 diabetes. Kumamoto study\textsuperscript{85} on comparing intensive treatment with insulin against conventional therapy in type 2 diabetes showed less microangiopathy in the former. Both DCCT & Kumamoto showed reduced incidence of microvascular complications by 50-70\% and demonstrated a non-significant trend towards reduction of macrovascular complications.\textsuperscript{76,84,85}

UKPDS33\textsuperscript{48} compared conventional (diet) and intensive glycemic control (sulfonylurea, insulin, metformin), net reduction of 0.9\% in HBA1c had been translated into 12\% fewer diabetes end points, 25\% reduction in microvascular events (p=0.0099), incidence of myocardial infarction was reduced by 17\% but with borderline significance.\textsuperscript{48} Metformin treated group had less mortality.\textsuperscript{77} Any abnormal HBA1c value is considered too high.\textsuperscript{76} The cut off point for optimal glycemia management was 7\% HBA1c.\textsuperscript{1,48,76,77,84,85}

UKPDS therapeutic decisions were made on FBG values that could explain at least partially the lack of effect on macrovascular events as recently accumulating data suggested beneficial effects with better control of non-fasting glucose excursions.\textsuperscript{1}

POSTPRANDIAL BLOOD GLUCOSE CONTROL

Nowadays little of the day is spent fasting and most of the times in postprandial or postabsorptive state. Wide fluctuations in plasma glucose levels may occur throughout the day with high values 1 to 2 hours after meal, so it is not surprising
that postprandial hyperglycemia is a greater contributor to blood glucose control than fasting.\textsuperscript{78} Jovanovic et al reported that the postprandial glucose at one hour is the best predictor of HBA1c in patients with well–controlled type 2 diabetes\textsuperscript{86}. Avignon A and associates showed that non-fasting plasma :2h postprandial and sustained postprandial (5 h) post lunch glucose levels are better predictor of overall glycemic control than fasting glucose. \textsuperscript{87}This was backed by a French study which showed stronger correlation between 2h post breakfast and HBA1c.\textsuperscript{88}

**Physiological background:**

Pulsatilie insulin secretion optimizes its action\textsuperscript{20}. It is secreted in two phases:

**Early- phase insulin release:**

Is a short and small burst released on food intake or increase in glucose plasma concentration, in the first 10 minutes.\textsuperscript{20,89} It represents the release of small pool of preformed and readily accessible insulin in secretary vesicles. This burst preempts and decreases the postprandial glucose elevation in the blood.\textsuperscript{20,78,89}

**Late- phase insulin release:**

More sustained release of insulin. It relies on mobilizing stored pool and/or de novo insulin synthesis.\textsuperscript{78,79,89}

The initial insulin release is lost early in type 2 diabetes and is an excellent predictor of both types of diabetes.\textsuperscript{89,90} Loss or attenuation of early-phase insulin release after a meal results in inadequate insulin suppression of hepatic glucose production.\textsuperscript{78,89} Initially extensive stimulation of the second phase ensues which leads to insulin resistance through down-regulation of the insulin post-receptors pathways on muscles and fat cells.\textsuperscript{89} Hence loss of early insulin burst results
in postprandial hyperglycemia, insulin resistance and progressive loss of insulin-producing cell in both types of diabetes. \textsuperscript{78,89,91,92}

**The effect of postprandial glucose on microvascular complications**

High blood glucose levels (postmeals) lead to increased synthesis of diacylglycerol, which jointly with intracellular calcium activate protein kinase C. The result is impaired contraction of smooth muscles (pericytes), increased production of basement membrane material, and enhanced cell proliferation and capillary permeability.\textsuperscript{93}

Activation of protein C, endothelial dysfunction and increased expression of vasoconstrictor endothelin could be responsible for microvascular complications that may be developing in the early stages of diabetes. \textsuperscript{89,91,94} Data from national health and nutrition examination survey showed that 2-hour postprandial glucose levels of 194 mg/dl had resulted in a threefold increase in retinopathy despite normal fasting blood glucose levels.\textsuperscript{18} Similar incidences were reported in studies of Pima Indian and Egyptian populations. Mohan et al reported the association of high postprandial glucose with diabetic nephropathy.\textsuperscript{89} Beghi et al showed its association with increased the prevalence of diabetic neuropathy.\textsuperscript{92}
Glycemic threshold for developing macrovascular complications is lower than that for microvascular. High postprandial blood glucose levels are associated with postprandial hyperinsulinemia, atherogenic lipids which heightened the occurrence of CHD.  

Postprandial glucose stimulates platelet aggregation and results in protein and cellular glycosylation. Glycosylated LDL particles are more easily oxidized, taken up by macrophages through scavenger system with resultant atherosclerotic plaque. Glycosylated HDL is less efficient in transporting cholesterol back to the liver than the normal HDL. In addition formation of advanced glycosylated end products in the collagen of the vessel wall may directly stimulate or accelerate the atherosclerotic process. It also stimulates free radicals, plasminogen activator inhibitor and endothelial dysfunction. Control of postprandial glycemia reverses this hypercoagulable state.

The Honolulu Heart Study found that the incidence of CHD was twice as high in patients with postprandial blood glucose levels between 157-189 mg/dl as in those with levels <140mg/dl. The incidence of sudden death was doubled with levels >151mg/dl. The Whitehall study of British male civil servants showed that 2h postprandial glucose levels of >196 mg/dl were associated with two fold increase mortality from CHD. The Islington Diabetes Survey reported double major CHD events when 2h postprandial was 120-180mg/dl (17%) as compared to levels <120mg/dl.
This had also been shown in the Paris Prospective Study. Hooran study documented that 2h postprandial glucose value was an independent risk factor for peripheral vascular disease. The Oslo study demonstrated that nonfasting glucose levels were predictors of fatal stroke in diabetic patients, risk increasing by 13% for each 18mg/dl elevations in postprandial glucose.

The Diabetes Intervention Study reported that postprandial not fasting hyperglycemia was an independent risk factor for myocardial infarction and cardiac death. The Helsinki Policemen Study revealed an independent association between fatal and nonfatal CHD and 1 h and 2hour postprandial insulin levels than that with fasting glucose.

When compared ladies with gestational diabetes with controlled postprandial glucose had lower HBA1c, lower birth weight of babies, less neonatal hypoglycemia and less caesarean section than preprandial controlled group. Combs et al, Demarini et al demonstrated higher incidence of macrosomia & neonatal hypoglycemia with high postprandial glucose. Consequently the ADA (American Diabetes Association) now recommends monitoring both fasting and 1hour plasma serum glucose levels during pregnancy.

**Control of Postprandial hyperglycemia**

Postprandial hyperglycemic control is important in avoiding diabetic complications, lowering insulin resistance ,restoring normal insulin secretion, and avoiding complications in the offspring's of women with diabetes. Methods that lower both fasting and postprandial glucose levels are recommended.

**Oral basal-bolus therapy:**
Patients with type 2 diabetes who require none or just an evening injection intermediate insulin to control the fasting glucose level, an oral agent capable of stimulating an insulin release sufficient to cover the meal or delay the absorption of glucose from intestine (bolus agent) should be used. In conjunction with oral agents that lower insulin resistance, decrease hepatic glucose production, or stimulate insulin production (basal agents).

**Injection basal-bolus therapy:** Type 2 diabetics who take insulin, need fast-acting lispro-like insulin as bolus therapy, even if they have some preserved endogenous production because they lack the first-phase insulin release.102,103

**Basal agents** include glitazones, metformin, long acting sulfonylureas, intermediate and long acting insulins.78,89-92 **Bolus drugs:** target postprandial hyperglycemia preventing hyperinsulinemia, postprandial hypoglycemia and weight gain. They include: acarbose, miglitol, repaglinide, lispro-like insulin and possibly glimepiride.78,89-92

**New agents that stimulate short-lived insulin release:**
D-phenylalanine derivative e.g nateglinide enhances insulin release in the presence of high glucose levels.78,89 Other group include amylin analogue pramlintide, glucagons-like insulinotropic polypeptide(GLIP), they slow gastric emptying and suppress glucagons production. Pramlintide replenishes glycogen stores; GLIP increases insulin production in response to a meal. It is easier to achieve the long term HBA1c goal <7% using basal-bolus therapy because the biggest contributor is the postprandial glucose.78,89-92

**Monitoring Glycemic Control**
The contemporary management of diabetes mellitus is based principally on frequent determinations of glycemic control via many methods:

**Self monitoring of blood glucose (SMBG)**

Implies frequent measurements of capillary blood glucose levels by diabetics. Blood is obtained by finger prick method and glucose measured with reagent strip or meter.\(^{104}\)

For oft-used fingers, stable patients should take few days off to let the fingers heal. Sites with fewer nerve endings like forearm can be used with newer devices, but if the patient prescribes results are unreliable.\(^{46}\) Results may be different from finger tip, in which changes in glucose after meal would be detected before forearm or thigh.\(^{105}\)

Veterans Affairs recommend that patients with stable type 2 on oral agents or diet perform SMBG twice weekly. Meier JL et al had shown that decreasing the frequency of SMBG (0.7 strips/patient/day), resulted in substantial cost saving (6.37 USD/patient/month) without affecting glycemic control.\(^{106}\) Similar results were shown in a cohort of 421 with paired GHbA1c data.\(^{106}\) In a review by Faas et al of studies on SMBG 1976-96 only one positive conclusion regarding its efficacy was found.\(^{107}\)

### 3. Non-invasive blood glucose monitoring

Two devices have been approved by FDA:

1. Minimed (Glucowatch): Uses intophoresis to assess glucose in interstitial fluids
2. Uses indwelling subcutaneous catheter to monitor interstitial fluid glucose
Both devices utilize immobilized glucose oxidase to generate electrons in response to changing glucose levels.\textsuperscript{7} These meters report the value 15 minutes delayed from serum level allowing just three readings per hour. They need to be calibrated regularly.\textsuperscript{7,38}

Metzger et al concluded that in real-life setting the accuracy of data provided by the Minimed may be less than expected and should be confirmed by independent means before clinical decisions are made.\textsuperscript{108}

3. Intensive glucose monitoring:

Some patients with perfect HbA1c or normal FBG develop complications. They are likely to have unstable diurnal variation with frequent excursions of high blood glucose at night. Unger recommended a 3-day continuous glucose monitoring; results showed that glucose levels were greater than 200mg/dl for many hours each day in the studied group.\textsuperscript{46} The Minimed glucose sensor allows continuous 72-hours glucose monitoring and represents a potentially important tool to improve the management of diabetes.\textsuperscript{46}

Long Term Monitoring

1. Glycosylated Haemoglobin

Glycated Hb (GHb) is derived from HbA, the major component of adult haemoglobin, which also consists of small amount of HbA2 and a trace of Hb F. Formation of GHb begins during erythropoiesis and continues through the 120 day lifespan of the red blood cells.\textsuperscript{7,16,38}
It is a post translational modification of haemoglobin. Non enzymatic reaction between free aldehyde group of glucose and the unprotonated form of free amino acid group of HbA. A labile aldimidine form is generated in the first fast reaction, then partially converted into a stable ketonamine form via amadoni arrangement.\textsuperscript{7,16,38,109}

There are various subfractions forms of glycated HbA including HbA1a, HbA1b and HbA1c. HbA1c is the most abundant form. Increased amount of HbA1c had been found in the serum of diabetics.\textsuperscript{16,24}

Since the formation of glycated Hb is irreversible and the level in the red cells depends on the concentration of blood glucose, a single HbA1c determination reflects the average glucose concentration for the preceding 8-12 weeks.\textsuperscript{7,48}

**Glycated haemoglobin analysis:**

Many tests to measure glycated haemoglobin are available. It is also desirable that all laboratories performing A1C testing participate in the College of American Pathologists proficiency testing survey for A1C testing started in mid-1996, which uses whole-blood specimens\textsuperscript{104}.

**Two commonly used tests are:-**

- **High performance liquid Chromatography (HPLC):**
  Is the most accurate method for estimating glycated HbA1c.\textsuperscript{7,38}

- **The Kit method:**
  Is based on the affinity the boronated groups have for cis-diol structures found in glycated protein. Glycated proteins are eluted from boronated columns and their absorbance determined on spectrometer.\textsuperscript{7,38,110} Normal values are 4-6% in nondiabetic.\textsuperscript{24,45}
For GHbA1 %: Over treatment is the level less than 6%, very good control is 6-8% & Good control is 8-9.5%. During pregnancy a figure of 8.5% is acceptable.45,66

For HbA1c %: normal value less than 6.5, acceptable level 6.5-7.5%, high risk greater than 7.5%.24,45,48,66 The A1C test has been shown to predict the risk for the development of many of the chronic complications in diabetes.24,49,101,104

Expert opinion recommends HbA1C testing at least two times a year in patients who are meeting treatment goals (stable glycemic control) and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycemic goals.38, 24, 44,45,104

3. **Glycated serum protein (GSP):**

Reflects average blood glucose control over preceding two weeks, albumin is the main component. Measurements of total GSP and glycated serum albumin (GSA) correlate well with one another and with measurements of glycated hemoglobin (A1C test).38,104

GSP assay may be of value when A1C test cannot be measured or may not be useful i.e hemolytic anemias or with short-term changes (1–2 weeks) in glycemic status. Several methods have been described that quantify either total GSP or total GSA. Fructosamine assay is widely used.104,107 Values for GSP vary with changes in the synthesis or clearance of serum proteins.104,107 Good control is stated to be < 2.7 mmol/L, Poor control > 3.5 mmol/L. These ranges are only correct when the albumin concentration is normal: 30-45 g/L.7,66

3. **Serum adenosine deaminase (AdA):**
AdA related to the proliferation and differentiation of lymphocytes is suggested to be an important modulating enzyme for the bioavailability of insulin. Mensah et al demonstrated a positive correlation between AdA and GHbA1 as a function of hyperglycemia. They suggested that under condition of uncomplicated diabetes ie. without any infections (which raises AdA), serum AdA activity may be used to monitor long term diabetic control. It is relatively cheaper and could be of value in situation where GHbA1 couldn’t be utilized.\(^\text{110}\)

**Comprehensive management of type 2 diabetes**

Holistic approach has been recommended by US National Institute of Health, Institute of continuous Improvement (ICI) and ADA goals for management to address dyslipidemia, hyperglycemia, high blood pressure, microalbuminuria, prothrombotic diabetic state, smoking cessation\(^7,24,46,111\):

**Dyslipidemia:** Goals are total cholesterol (TCH) < 200mg/dl, TG < 150mg/dl, HDL >45mg/dl, LDL <100mg/dl. These could be achieved through diet, fibrates and statins for TG, HDL and statins for LDL. Statins reduced CVD events by 15-20%.\(^{46,111}\)

**High blood pressure**

Multiple studies showed greater absolute benefit from controlling blood pressure; HOT study targeted diastolic\(\leq 80\)mmHG demonstrated 50% reduction in CVD events.\(^{111}\) Targeting systolic B.P \(<130\) resulted in 50% further reduction in mortality.\(^{46,111}\) Patients with renal insufficiency or proteinuria \(>1-2\)gm/24hours B.P target \(<120/75\).\(^{24,56}\) Preferred first line is ACE-I, ARB; usually combination of drugs required\(^{46,48,112}\) Aspirin together with statin resulted in 15-20% reduction in CVD events.\(^{46,111,113}\)
Steno-2 trial had made it clear that intensive multiple risk factors approach in patients with microaluminuria would result in 50% reduction in macrovascular and microvascular events as compared to conventionally managed group. Their targets were: HbA1c<6.5%, BP<13/80, fasting TCH<170, TG<150 mg/dl.

All patients received aspirin. Curves representing time to first event for the two groups continued to diverge throughout follow up for 8 years. \textsuperscript{114} HOPE study showed that ACE-I decreased CVD events by rate of 25% inpatients without microalbuminuria. \textsuperscript{111}

\textbf{Prevention of diabetes}

Diabetes is chronic, progressive and degenerative. Its onset can pre-date the diagnosis by up to 10 years. Up to 20% of patients have detectable retinopathy at diagnosis. Tuomilehto et al (the Finish trial) have shown that effective life style changes (changing overweight, central obesity, physical inactivity, high fat and energy diets) can prevent diabetes and improve quality of life. \textsuperscript{115} After 4 years, the lifestyle intervention group had reduced the risk of developing type 2 diabetes by more than 50%, despite a modest average weight loss of 7lbs or less than 5% total body weight. \textsuperscript{116} In US Diabetes Prevention Programme (DPP) subjects who changed their lifestyle had reduced their risk of developing type 2 diabetes by 58%
The lifestyle intervention was effective for subjects of all ages and ethnic groups. Subjects with standard care (no lifestyle intervention) plus metformin reduced their risk of getting type 2 diabetes by 31 %. How would this interesting intervention be applied in health delivery system remains to be designed to help reducing one major chronic disease of our century.
OBJECTIVES OF THE STUDY

-To explore the relations among blood glucose levels at different times related to breakfast; fasting (FBG), 2 hour (2HPBG), 3 hour (3HPBG) post breakfast.

-To examine the relationship between HbA1c and Blood glucose levels at fasting, two hour and three hour post breakfast.

-To evaluate the power of each blood glucose test in inferring glycemic control when correlated to HbA1c.

-To study the relation between postprandial glycemia and occurrence of long term complications of diabetes.

-To study the effect of oral antidiabetic on different blood glucose parameters

Study Design and methods:
Our study is an outpatient based cross sectional; descriptive and comparative study. It was carried in the period September 2002-May 2003, at Gaber Abuelez diabetic center, situated in Khartoum 2 about two kilometers south to Khartoum teaching Hospital. Registered diabetics were 9224, with a daily flow of 40-50 patients, around 10-15 were new cases. From those attending the diabetic clinic 99 Sudanese patients diagnosed with type 2 diabetes were selected by the study investigator. Sample size was calculated according to the formula:

\[ N = \frac{z^2 \cdot PQ}{d^2} \]

, z: CI: 1.96=95% in the z table

P: prevalence =5% , the maximum for diabetes in northern Sudan. q: 1-p, d: design defect =0.0025

The selected patients had satisfied the selection criteria of being on no- insulin treatment; no change in treatment or life style within the three months before the study; no concomitant chronic disease or recent acute illness; and willingness to return to the clinic three times in one day, three times in one month to measure blood glucose. Those with diabetes diagnosed within the previous 6 months & pregnant ladies were excluded. They had given their informed consent.

Of the total 99 enrolled (45% men and 55% women) 68 completed the study. The mean age was 55.66±9.86, duration of diabetes averaged 8.91±7.31 years. Treatment consisted of diet only in 18.2% of patients, sulfonylurea in 58.6%, metformin in 4.1% and combination of both metformin and sulfonylurea in 19.1%.
Methods: Patients taken randomly were interviewed using a pre-tested and pre-coded questionnaire and check-list for physical examination. Each patient came to the diabetic clinic in the morning (8-8:30) after 10-to14 -hour overnight fast. At the time venous blood was withdrawn to measure blood glucose. The patient then returned to the clinic to measure blood glucose 2h after breakfast (10-10:30), then 1 hour later (3h) (11:30-12:30) .The process was carried out three times (7-14 days apart) over one month period at the end of which venous sample withdrawn and HBA1c was measured according to specified protocol118. Serum cretinine, Hb, urine general, ECG were done.

Patients were asked to follow their usual treatment and eat their usual diet during the study duration. Patients past glucose profiles were reviewed; however only few had done both FBG&2HPBG.

Patients who failed to show up were phoned and asked to return. Those who didn't show up were substituted.

Analytical determinations:

Blood samples were centrifuged within 1hour after blood withdrawal for immediate assessment of blood glucose (using gluco-oxidase: GOD; Enzymetic colorimetric test, GOD-PAP method, CRESCENT DIGNOSTICS,KSA). Blood for HbA1C was kept in EDETA containing bottles at 8º C. HbA1c was measured within 3-7 days using HbA1C chromatographic-spectrophotometric, Ion exchange-Temperature independent, biosystems reagents & instruments, Germany. Spectra model 270, spectrophotometer Sherwood, Cambridge, England. was used to read the values of glucose, HBA1C, creatinine.
**Statistics:**

Standard procedures were used to calculate the means, SD, SEM and simple correlation coefficients. Analysis of variance, $\chi^2$ tests, paired t test, ANOVA, multivariate logistic analysis multiple linear regression analysis were used. In the latter, fasting glucose and all the postprandial glucose levels were included as explanatory variables for HbA1c.

The cut off point for good glycemic control was 7% for HBA1c, 6.6mmol/l (120mg/dl) for fasting glucose, 160mg/dl (8.9mmol/l) for postprandial glucose. Accordingly an increase $>2.2$mmol/l(40mg) in glucose levels 2h/3h after the meal was regarded as exaggerated. Correlation significance and independence among fasting, 2&3h glucose were evaluated. Software SPSS programme was used in statistical analysis.
RESULTS

Demographic data:

A sample of 99 diabetic patients was studied. 56% were females (Figure 1). The average age was 55.6 years +/- 9.86. The most frequent age was 45. 76.9% were more than 45 years (Figure 2).

Figure 3 shows the residence of patients. The majority were coming from Khartoum. Most of the patients were of low socioeconomic status.

Figure 4 shows the tribal distribution of the patients. The most common tribe is gaaleen which represented 26.2%, followed by danagla 12.6%, mahsi 11.6, the rest of Arab dominant tribes constituted 32.4%, and the rest (<20%) were from the West and South.

Figure 5 presents the education status of the patients. Less than 10% had high school education or above.

Clinical Features:

Figure 6 shows the distribution of patients according to their body mass index. The average BMI was 27.4947 +/- 4.54 kg/m². 65.5% of patients were overweight or obese. Obesity (BMI > 30) occurred in 31.1%.

Figure 7 presents types of treatment used by the studied group. Sulfonylurea was the first line of therapy; more than 50% of patients were using the drug. Only 4% was using metformin.

Family history of diabetes was found in 68.7%. Distribution of paternal and maternal antecedence was 33.3% and 25.5% respectively, a quarter had at least one sibling with diabetes.
**Diabetic Complications:**

Hypertension was demonstrated in 42.2% but those with history and/or on treatment was 21.4%. History of DKA was reported in 7.1%. Hypoglycemic episodes occurred at higher rate 12.1%, nevertheless only one case necessitated hospitalization.

Table 1 shows the prevalence of complications in the studied group: cataract was seen in 13.2% with a trend towards increasing with increase in the duration of diabetes. Retinopathy was found in 24% of patients, in 8.15% was proliferative. 11.1% reported receiving photocoagulation. Poor correlation was seen between complications, presence of hypertension and the magnitude of hyperglycemia.

Neuropathic complaint was reported in 29.3% but abnormal sensation demonstrated in only 10.1%. There was a trend of increasing prevalence with longer duration of diabetes. It doubled at every five years increase, albeit no significant difference was shown between 10-15 and more than 15 years (P=<0.05).

Significant drop in blood pressure was shown in 16.2%. A similar percentage occurred for erectile dysfunction. Nearly 80% was known diabetic for more than 10 years. No relation to high blood pressure was found.

Overt proteinuria wasn't shown in this sample nor was past history of nephropathy. All patients had normal creatinine values. However when Crocroff-Gault formula was used to calculate creatinine clearance (CC), the average CC was 96.95 +/- 28.323 ml/min. 10.8% showed value of less than 60 ml/min. 24.3% had a value that fall in the range of renal insufficiency (60-85ml/min).

Diabetic foot mainly septic (DSF) was reported in 10.1%.
4% were being treated for CHD. Of the 24% who brought forth their ECG, positive findings shown in 5.7% mainly features of left ventricular hypertrophy (LVH) & premature ventricular ectopics (PVE).

No evidence of peripheral, carotid disease or TIA/stroke was found in this group of patients.

**Behaviour of patients towards their disease**

16.4% admitted to smoke. 62.5% smoked more than 10 cigarettes a day. 75.8% claimed checking regularly their blood glucose. However, one third did that on feeling bad and 8% did it twice per month. Half of the patients (50.7%) measured their blood glucose. Blood glucose control was poor and a few managed to show persistence for more than a year.

Only one third kept records of follow up (30.3%); 91% of them measured fasting blood glucose and just 9% had done 2 hours postprandial blood glucose. Satisfactory control was shown in 26.4% very much in agreement with the study measurement (73.7% had FBG values more than 140 mg/dl). 14% from the studied group owned glucometers but a few used it for SMBG, among reasons forwarded were their doubts in its reliability and being advised by their treating doctors against its goodness. A good number did not know how to use.

From the 99 patients only 3% had measured their HbA1c and that was for one time. The majority of the patients were not aware about it. Lipid profile hadn't a better stance as only 6.1% had measured their lipids.

Adherence to therapy was generally good, being higher for medication (84.4%) and less so for diet (69.7%)

**Glucose profiles**
Blood glucose averaged 174.12 +/- 59.79 mg/dl (9.67 mmol/l) in the fasting state, 2h after breakfast was 247.1 +/- 72.072 mg/dl (13.72 mmol/l) and at 3h was 224.49 +/- 76.84 mg/dl.

Blood glucose was significantly lower in the fasting than the fed state.

Most patients 79.4 % had glucose level of >120 mg/dl before breakfast (FBG), only 20.9% (n=14) showed good control ( <120 mg/dl ). Most patients had blood glucose level >160 mg/dl post meal: 91.2 %(62) at 2h after breakfast, only 8.8%(6) showed satisfactory postprandial control. 87.3% showed value >160 mg/dl at 3h after breakfast in single determination, whereas in mean values (three readings over one month time) the percentage was 70.6%(48), 29.4% showed values <160 mg/dl (20). When the cut off point for three hour post breakfast was reduced to 140 mg/dl, 83.8%(57) of patients recorded blood glucose value more than 140 mg/dl, 16.2%(11) <140 mg/dl. Among patients with FBG less than 120 mg/dl (20.6%), 82% had levels more than 160 mg/dl after 2h, 29.4% had levels more than 160 mg/dl after 3h from breakfast, and the percentage went to 70% for 3h levels more than 140 mg/dl.

The average absolute increase in blood glucose 2h, 3h after breakfast (over the fasting blood glucose levels) was 73.0098 +/- 40.1855 mg/dl and 50.370 +/- 41.846 mg/dl respectively.

The frequency of distribution showed that blood glucose excursion 2h after breakfast was >40 mg/dl in 79.4% of patients, whereas that of 3h post breakfast was in 55.4%. The difference in glucose values at 3h and 2h following breakfast averaged 22.6397 +/- 33.5477 mg/dl; favoring the 2h which was higher than 3h glucose in 80% of samples.
**HBA1c:**

HBA1c averaged 8.474%+/−1.9 7. We found that 25% of patients had values less than 7%. Among them 47.05% had fasting glucose more than 120mg/dl, 82% 2h excursion more than 40mg/dl and 29.4% excursion more than 40mg/dl at 3h postbreakfast.

**Correlations:**

Table 2, 3 reports the simple correlations among blood glucose levels at different times related to breakfast. That between FBG & 2h was 0.830 for the average means, when computed at single determination it was 0.82 (p<0.0000), between FBG & 3h was 0.841, between 2h & 3h approached one in single determination 0.912 (p<0.0000)& 0.900 for the average means. All of the correlations were highly significant but that between 2h&3h and fasting wasn't particularly strong for average means.

Table 4, 5 presents simple correlations between HBA1c and blood glucose at different times related to breakfast. The correlation coefficients were significant between fasting and 3 hour post breakfast and HbA1c at r= 0.601 and 0.547 (p<0.000) respectively.

The relationship between the fasting glucose levels and HbA1c was particularly strong. The correlation between HBA1c and changes of glucose at 2 hours after meal was weak but positive correlation was shown at single determination.
Table 6 presents correlations among glucose excursions. It shows the significant increase of glucose from the fasting value at 2&3 h, and the changes at 3 h from the glucose levels at 2 h. The correlation between glucose excursion at 2h and 3h was strong r= 0.666(P=0.000). The excursion between 2h &3h has half the r value of 2h glucose excursion r=0.367(P=0.002). Negative correlation was found between glucose excursion at 3h post breakfast and the excursion between 2h &3h r=0.449(p=0.000). Paired T test for glucose excursions at 2h and 3 h post breakfast is shown in (table 7). Paired T test of different blood glucose levels showed that the difference between FBG and 2h post breakfast glucose when grouped and when paired is significant (t = 14.982,p= 0.000, CI: 95%). Also the differences between 3 h post breakfast glucose and FBG(9.926;p = 0.000). The difference in values of 2h&3h was significant but t value was remarkably low( t = 5.565,p= 0.000). Although differences were significant, 2h increased by 22.64mg/dl more than 3 h glucose, the maximum difference never exceeded 30 mg/dl and the lower was 14.59 mg/dl; confidence interval was 95%. In less than 10% of patients 3h glucose was more than 2 h glucose. The correlation between the two values was 0.900.

Table 8 shows the relationship among blood glucoses at different times related to breakfast. It presents their values in predicting glycemic control when the glycated haemoglobin was taken as the standard; control was classified as good when the value of HbA1c is less than 7% and poor when it exceeds 8.5%.

Table 9 summarizes the main clinical features of diabetes including different glucose parameters correlated to different types of treatment. The duration in males averaged 11.4 years, that in females was shorter with a mean of 6.91 years.
Table 10 shows the correlation between long term diabetic complications and the different parameters of blood glucose control using ANOVA, no significant association had been demonstrated.
Figure (1)
Distribution of sex patients
In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003

44% Male
56% Female
Figure No. (2)
Patients Age distribution
In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003
Figure No.(3)
Patients distribution according to residence
In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003

Khartoum Omdurman Khartoum North Other states

In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003
Figure (4)
Patients Distribution According To Tribe
In Non-insulin-Treated Type Two Diabetes
In Khartoum State 2003

- Gaali: 23
- Mahasi: 11
- Donglacy: 12
- Others: 53
Figure No. (5)
Patient Education
In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003
Figure No. (6)
Prevalence of Obesity
In Non-Insulin-Treated Type Two Diabetes
In Khartoum State 2003

Under weight: 2%
Ideal: 32%
Over weight: 35%
Obese: 31%
Figure (7)
Treatment OF Type Two Diabetic Patients
Khartoum State 2003

Table (1)
Prevalence of long term complications in non-insulin treated type 2 diabetic patients-Khartoum 2003

<table>
<thead>
<tr>
<th>Cataract</th>
<th>Retinopathy</th>
<th>Neuropathy</th>
<th>CHD</th>
<th>Diabetic foot</th>
<th>Postural hypotension</th>
<th>Erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1%</td>
<td>24%</td>
<td>10.1%</td>
<td>5.7%</td>
<td>10.1%</td>
<td>16.1%</td>
<td>16.3%</td>
</tr>
<tr>
<td>13.1%</td>
<td>11.1%</td>
<td>29.1%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHD: Coronary heart disease. ED: erectile dysfunction. Exam: Clinical examination

Table (2)
Simple correlation of blood glucose levels at different times related to breakfast in non-insulin treated type 2 diabetes – (single determination)-Khartoum 2003

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG vs.2hPBG</td>
<td>0.820**</td>
<td>0.000</td>
</tr>
<tr>
<td>3hPBG vs.FBG</td>
<td>0.727**</td>
<td>0.000</td>
</tr>
<tr>
<td>3hPBG vs.2hPBG</td>
<td>0.912**</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Correlation is significant at 0.01 level (2-tailed). FBG: Fasting blood glucose, 2hPBG: Two hour post breakfast blood glucose, 3hPBG: Three hour post breakfast blood glucose

Table (3)
Simple correlation of blood glucose levels at different times related to breakfast in non-insulin treated type 2 diabetes – Khartoum -2003

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG vs. 2hPBG</td>
<td>0.830**</td>
<td>0.000</td>
</tr>
<tr>
<td>3hPBG vs. FBG</td>
<td>0.841**</td>
<td>0.000</td>
</tr>
<tr>
<td>3hPBG vs. 2hPBG</td>
<td>0.900**</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed): Means were used to determine the values. FBG: fasting blood glucose, 2hPBG: two hours post breakfast blood glucose. 3hPBG: three hours post breakfast blood glucose.

Table (4)
Simple correlation between HbA1c and blood glucose levels at different times related to breakfast in non-insulin treated type 2 diabetes (Single determination)–Khartoum -2003

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c vs. FBG</td>
<td>0.584**</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c vs.3hPBG</td>
<td>0.649**</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c vs.2hPBG</td>
<td>0.669**</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Correlation is significant at 0.01 level (2-tailed). FBG: Fasting blood glucose. 2hPBG: Two hour post breakfast blood glucose. 3hPBG: Three hour post breakfast blood glucose.
Table (5)

Simple correlation between HbA1c and blood glucose levels at different times related to breakfast in non-insulin treated type 2 diabetes –Khartoum -2003

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c vs.FBG</td>
<td>0.601**</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c vs.2hPBG</td>
<td>0.202</td>
<td>0.102</td>
</tr>
<tr>
<td>HbA1c vs.3hPBG</td>
<td>0.547**</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Correlation is significant at 0.01 level (2-tailed). Means were used to determine the values. Correlation is significant at the 0.01 level (2-tailed):

FBG: Fasting blood glucose, 2hPBG: Two hour post breakfast blood glucose.
3hPBG: Three hour post breakfast blood glucose
Table (6)

Glucose excursions in non – insulin treated type 2 diabetics Khartoum 2003

<table>
<thead>
<tr>
<th>Glucose excursions relations</th>
<th>Correlations:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 2 hours (FBG – 2hPBG) vs. 3 hours (FBG- 3hPBG).</td>
<td>0.666</td>
<td>0.000</td>
</tr>
<tr>
<td>2 hours vs. (3hPBG-2hPBG)</td>
<td>0.367</td>
<td>0.002</td>
</tr>
<tr>
<td>3 hours (3 hPBG- FBG) vs. (3h BG-2hPBG)</td>
<td>-0.449</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Correlation is significant at 0.01 level (2-tailed). FBG: Fasting blood glucose, 2hPBG: Two hour post breakfast blood glucose, 3hPBG: Three hour post breakfast blood glucose
Table (7)

Paired T test for glucose excursions at different times related to meals in non – insulin treated type 2 diabetics -Khartoum 2003

<table>
<thead>
<tr>
<th></th>
<th>FBG vs. 2 h BG (n=67)</th>
<th>2 hPBG vs. 3 hPBG (n=67)</th>
<th>3 hPBG vs. FBG (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired difference</td>
<td>73.010+/- 0.185mg/dl</td>
<td>22.64+/- 33.54mg/dl</td>
<td>50.370+/- 41.846mg/dl</td>
</tr>
<tr>
<td>SEM</td>
<td>4.873</td>
<td>4.068</td>
<td>5.075.</td>
</tr>
<tr>
<td>C.I 95%</td>
<td>63 – 82.283 mg/dl</td>
<td>14.519 – 0.760mg/dl</td>
<td>40.241–60.455 mg/dl</td>
</tr>
<tr>
<td>T test</td>
<td>14.982</td>
<td>5.565</td>
<td>9.926</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Correlation is significant at 0.01 level (2-tailed). CI: Confidence interval  SEM: Standard error of the mean. FBG: Fasting blood glucose. 2hPBG: Two hour post breakfast blood glucose.3hPBG: Three hour post breakfast blood glucose
The relationships among blood glucoses at different times related to Breakfast in non–insulin treated type 2 diabetics – Khartoum 2003

<table>
<thead>
<tr>
<th>HbA1c N = 67</th>
<th>Less than 7% N=17</th>
<th>7 – 8.5% n=20</th>
<th>More than 8.5% n = 30</th>
<th>Tests</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG&lt;120mg/dl</td>
<td>9 (529%)</td>
<td>3 (15%)</td>
<td>2 (6.66%)</td>
<td>Pearson x²</td>
<td>0.00</td>
</tr>
<tr>
<td>FBG&gt;120mg/dl</td>
<td>8(47.88)</td>
<td>17 (85%)</td>
<td>28 (93.3%)</td>
<td>Likelihood ratio Linear/linear association</td>
<td>0.00</td>
</tr>
</tbody>
</table>

| 2 h excursion | < 40 mg/dl | 3(17.64%) | 2 (10%) | 1 (3.33%) | Pearson x² | 0.25 |
|---------------|------------|-----------|--------|-----------| Likelihood ratio Linear/linear association | 1  |
|               | >40 mg/dl  | 14(82.35%)| 18(90%)| 25(96.66%)|                                      | 0.24 |

| 3h Excursion  | <40        | 12(70.58%)| 6 (30%) | 2 (6.66%) | Pearson x² | 0.00 |
|---------------|------------|-----------|--------|-----------| Likelihood ratio Linear/linear association | 0  |
|               | > 40       | 5 (29.4%) | 14 (70%)| 28 (93.3%)|                                      | 0.00 |

Correlation is significant at 0.01 level (2-tailed). FBG: Fasting blood glucose, 2hPBG: Two hour post breakfast blood glucose. 3hPBG: Three hour post breakfast blood glucose. HbA1c: glycated hemoglobin
Table (9)

Main features and glucose parameters correlated to treatment in non-insulin treated type 2 diabetic patients -Khartoum 2003

<table>
<thead>
<tr>
<th>N=68</th>
<th>Diet</th>
<th>SU</th>
<th>MET</th>
<th>MET +SU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>AGE (Years)</td>
<td>55.86</td>
<td>510</td>
<td>56.84</td>
<td>55.85</td>
<td>60</td>
</tr>
<tr>
<td>Duration of diabetes (Years)</td>
<td>8.14</td>
<td>5.6</td>
<td>11.92</td>
<td>6.84</td>
<td>1.5</td>
</tr>
<tr>
<td>BMI</td>
<td>25.84</td>
<td>29.6836</td>
<td>24.9482</td>
<td>28.014</td>
<td>25.6029</td>
</tr>
<tr>
<td>FBG mg/dl</td>
<td>107.30</td>
<td>144.556</td>
<td>173.850</td>
<td>173.850</td>
<td>158.25</td>
</tr>
<tr>
<td>2HBG mg/dl</td>
<td>175.967</td>
<td>202.83</td>
<td>246.158</td>
<td>252.758</td>
<td>262</td>
</tr>
<tr>
<td>3HBG mg/dl</td>
<td>138.987</td>
<td>183.722</td>
<td>223.67</td>
<td>23.4.652</td>
<td>241.083</td>
</tr>
<tr>
<td>Hb A1c %</td>
<td>5.760</td>
<td>8.233%</td>
<td>8.62</td>
<td>8.436</td>
<td>8.9</td>
</tr>
</tbody>
</table>

BMI: body mass index. Average duration in females is 6.91 years. Average duration in males is 11.41 years. FBG: Fasting blood glucose. 2hPBG: Two hour post breakfast blood glucose. 3hPBG: Three hour post breakfast blood glucose. HbA1c: glycated hemoglobin. SU: sulfonylurea. MET: Metformin. Correlation is significant at 0.01 level (2-tailed).
Correlation of Long term diabetic complications with different glucose parameters in non-insulin treated patients with type 2 diabetes- Khartoum 2003

<table>
<thead>
<tr>
<th></th>
<th>N=68</th>
<th>FBG</th>
<th>2hPBG</th>
<th>3hPBG</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic retinopathy</td>
<td>0.762</td>
<td>0.127</td>
<td>0.236</td>
<td>0.181</td>
<td></td>
</tr>
<tr>
<td>Somatic neuropathy</td>
<td>0.655</td>
<td>0.391</td>
<td>0.962</td>
<td>0.226</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.593</td>
<td>0.218</td>
<td>0.433</td>
<td>0.933</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0.468</td>
<td>0.661</td>
<td>0.362</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>Diabetic foot</td>
<td>0.793</td>
<td>0.673</td>
<td>0.617</td>
<td>0.749</td>
<td></td>
</tr>
</tbody>
</table>

FBG: Fasting blood glucose. 2hPBG: Two hour post breakfast blood glucose. 3hPBG: Three hour post breakfast blood glucose. HbA1c: glycated hemoglobin. CHD: coronary heart diseases.
**DISCUSSION**

**Demographic data:**

In studied group of 99 females represented 56% which agreed with literature. Elmahadi showed 65% predominance. Age averaged 55.6 years \(\pm 9.86\), 76.9% was more than 45 years. Majority of patients resided in Khartoum. Most patients were of low socioeconomic status, this may indicate that diabetes is becoming more popular among the poor in contrast to literature: diabetes is common in the poor sector of affluent countries but in the rich in underdeveloped or the fact that most of the rich go to private centres weaken this conclusion. The most common tribe is gaaleen at 26.2%, followed by danagla and mahas 12.6%, 11.6, Bagir et al demonstrated danagla tribe to be most affected with diabetes (8%) than other northern tribes. western, southern tribes constituted less than 20% much in agreement with Bagir et al. Vast majority of patients had received not more than primary education which would have negative impact over the management of diabetes which became more complex in recent years.

**Clinical Features:**

Most of the patients are overweight or obese with BMI mean of 27.4947 \(\pm 4.54\) kg per square metre, 65.5% of patients were overweight & 31.1% obese. Females are more inflicted by obesity; these approximated figures in literature. Elmahadi et al reported figure of 46.2%.

Obesity is on increase in Sudan and could be responsible for the increasing prevalence of diabetes type 2, which has reached epidemic rates world wide as direct result of improvement in people income and westernization of life style.
NICE guidelines recommend\textsuperscript{113} the use of orlistat (Xenical) when BMI exceeds 28 and the patient manages to lose 2.5 kg on diet in order to improve control of diabetes. Most oral hypoglycemic drugs cause gain in weight, less so is metformin which was used alone in 4% of our patients and in 19% in combination with sulphonylureas. Sudanese diabetic with type 2 are increasingly obese/overweight metformin should be the first line treatment. Use of weight lowering interventions including orlistat should be strongly considered.

Family history of diabetes was found in 68.7% near to 63% demonstrated by Elmahadi.\textsuperscript{44} Distribution of paternal and maternal antecedence was 33.3% and 25.5% respectively, a quarter has at least one sibling with diabetes. This goes well with other studies and supports the heritable component of type 2 diabetes but leave the question open for a third of patients with no family history of diabetes.\textsuperscript{8,44}

**Diabetic Complications:**

Hypertension was demonstrated in 42.2%, but only half of them were known to have hypertension (previously diagnosed and on treatment). This is similar to that reported by Ahmed M el-B\textsuperscript{44,121} but less than that reported by Elmahadi (12.9%).\textsuperscript{17} It comply well with that reported in UKPDS\textsuperscript{48} and other studies.\textsuperscript{49,50} Hypertension affects at least half of patients with diabetes.\textsuperscript{49}
In UK prospective diabetes study tight blood pressure control (mean 144/82 mm Hg) achieved significant reductions in the risk of stroke (44%), heart failure (56%), and diabetes related deaths (32%), as well as reductions in microvascular complications (for example, 34% reduction in progression of retinopathy). One third of patients required three or more antihypertensive drugs to maintain a target blood pressure <150/85 mm Hg. Ahmed failed to demonstrate significant correlation with age, duration of diabetes or nephropathy. Obesity could contribute to the high prevalence of hypertension in Sudanese diabetics.

History of ketoacidosis (DKA) was reported in 7.1% which is less than that reported but it reminds of the importance of type 2 in the events of DKA. Hypoglycemic episodes occurred at higher rate 12.1% but hospitalization was needed in one case. Cataract was seen in 14.1% as compared to cataract (16%) reported by Elmahadi et al with a trend towards increasing incidence with increase in duration of diabetes (p=0.09).

**Microvascular complications:**

Retinopathy found in 24% of patients; higher than that reported by Elmahadi (17.4%) , proliferative type was seen in 8.15% despite 11.1% who reported receiving photocoagulation. This could point to the reduced sensitivity of direct ophthalmoscopy in the diagnosis of retinal changes in the diabetics. ICI, NICE and ADA recommend the use of both ophthalmoscopy and retinal photography on annual basis to detect retinal changes in diabetics; together they give sensitivity of a round 70%. 7,8,16,24,45,49
Poor correlation was shown with duration of diabetes, age of patients, fasting and 2h glucose values but significantly correlated to presence of hypertension, HbA1c and 3h postbreakfast blood glucose (p<0.05). Neuropathic complaint is the commonest events being 29.3% however signs of peripheral neuropathy was demonstrated in only 10.1% in variance with Elmahdi 31.5%. The discrepancy between symptoms and physical findings could be explained by the prevailing hyperglycemia which could account for neuropathic pains. Nerve conduction studies would have been more plausible in truly estimating the prevalence of peripheral neuropathy in type 2 diabetes. There was a trend towards increased prevalence with prolonged duration of diabetes, prevalence doubled with every five years increase, albeit no significant difference was shown between the group of 10-15 years and more than 15 years (P=0.17).

Overt proteinuria wasn't shown in this sample nor did patients give history of nephropathy. The study wasn't powered to estimate prevalence of incipient nephropathy. Elmahdi reported figure of 9.2%. All patients had shown normal serum creatinine values. However when Crocroft-Gault formula was used to calculate creatinine clearance (CC) as an acceptable reflection of GFR 10.8% had value of less than 60ml/min, 24.3% had fallen in the range of renal insufficiency (60-85ml/min). This highlights the hazard of taking creatinine as screening test for renal dysfunction and that overt proteinuria doesn't on its own put subjects out of risk nephropathy. We recommend using this formula to estimate CC in the annual assessment for diabetics, it is simple &has high sensitivity.
Autonomic neuropathy was common as evidenced by significant postural drop in blood pressure and erectile dysfunction (ED) in 16.2%. Nearly 80% was known diabetic for more than 10 years, significant correlation to duration of diabetes was found (p<0.05) but no significant association to high blood pressure or degree of glycemic control. Awad & Ahmed\textsuperscript{123} had reported higher prevalence of autonomic neuropathy 40%, peripheral neuropathy in 66%; but their study included both types of diabetes and insulin treated type 2 with longer duration (mean = 16+/−7.3 years) and perhaps severer disease.

The prevalence of ED was probably higher due to under reporting. Erectile dysfunction is a common complication of diabetes, occurring in up to half of men aged over 50 years (compared with 15-20% in age matched non-diabetic men). It is of multifactorial aetiology non of the patients received any counseling or treatment despite the introduction of sildenafil in our market, which is reported to have a 50-70% success rate in patients with diabetes.\textsuperscript{49}

**Macrovascular complications**

Diabetic foot mainly septic (DSF) was reported in 10.1%, however clinical evaluation revealed no evidence of carotid stenosis or TIA/stroke in this group of patients.

Peripheral vascular disease and cerebrovascular disease were reported to be 3.4%, 4.4% in Elmahdi & Mukhtar.\textsuperscript{44} Elmahdi et al reported higher incidence of PVD of 6.2% in another study but patients were insulin treated.\textsuperscript{17}
Coronary heart disease (CHD) was shown by history in 4% compared to 5.1% reported by Elamahdi.\cite{44} Of the 24% who brought forth their ECG's positive findings were found in 5.7% mainly LVH, PVE and T wave inversions in anteriolateral leads.

Macroangiopathic complications were significantly related to aging and hyperglycaemia. The absence of correlation between postmeal glycemia and cardiovascular complications in our study could be explained by the small number of patients who had CHD as the relation was well documented.\cite{89,90,91,92,93,94}

**Behaviour of patients towards their disease**

Smoking was common among the group (16.4%). 62.5% smoked more than 10 cigarettes a day. This adds much to the already heightened risk of vascular complications and should be targeted as cutting smoking resulted in 50% reduction of all cause mortality and morbidity\cite{24,49,113}.

Monitoring of glycemic control in this group of patients was far from ideal as one third checked their blood glucose on feeling bad and only 8% did that twice per month. Half of patients (50.7%) did it monthly, however their glucose control was poor and few managed to show persistence for more than a year. Only one third had kept records for follow up (30.3%).

The practice at the centre is to monitor fasting blood glucose or random glucose (91%) plus urine for sugar. 2hour post breakfast glucose was done scarcely (9%). More than two thirds of patients had poor glycemic control. Very much in agreement with glucose measurements of the study.
14% from the studied group owned glucometers but few used it for SMBG, among reasons forwarded were their doubts in its reliability and being advised against it by the treating doctors. An appreciable number didn't know how to use it. This reflects poverty of knowledge among patients and doctors alike, more health education is needed to address these points. HbA1c was obviously wasn't acknowledged as method for glucose control; only 3% had ever measured HbA1c and for one time. Majority of patients were not aware about it. Its expense at 2500 Sudanese Dinars (9.5 $) further limits its utilization. Lipid profile wasn't better as only 6.1% had measurement, again translating major deviation from guidelines in Sudan specialized diabetic centre.

Adherence to therapy was generally good, being higher for medication (84.4%) but less for diet (69.7%). More than half of patients were using sulphonylureas, a round 20% on combined metformin and sulphonylureas and only 4% on metformin alone. Correlation between the type of treatment and BMI is poor. No patient is using any drug that targets postprandial glucose.

**Glucose profiles**
Most diabetic patients with apparently good control as inferred from HbA1c <7%, or by fasting <6.6% (120mg/dl) had indeed high glucose levels after meals and/or exaggerated glucose excursions following meals reaching unexpectedly high levels. In these patients one should consider using medications that are particularly effective in blunting postprandial glucose bursts.

The study indicated that monitoring glycemic control and efficacy of treatment cannot be restricted to fasting glucose and HbA1c. Both of which are poor indicator of blood glucose levels at different times of the day especially postprandially. 46,87-88

3 h postbreakfast glucose which wasn’t assessed on its own in similar studies has proved a significant association with fasting, 2h post breakfast and HbA1c. Its relation to 2h was particularly strong at single determination, however less strong when the means of the two tests were computed (0.912, 0.900 respectively). When means of values were computed the association was mildly stronger with the fasting values. Glucose excursion at 3 hours was significant and high with similar values and strength as that shown by Bonora et al 120 at 3h post lunch and 3h post dinner. Its significance is comparable to that obtained at similar timing shown by Lerman (prelunch). 88 3 h postbreakfast glucose could be an additive armamentarium in the array used in following glycemic control and could be used as an alternative to 2h and fasting, further studies are needed however.
Avington\textsuperscript{87} and a French study had proved the strength of extended postprandial glucose (5 hour post lunch) in predicting glycemic control and had shown it to be similar in power to 2 h post meal. Our study signaled out another option that is near in timing to the gold standard test preprandial (prelunch).\textsuperscript{1,88,119} Controlling fasting glucose alone ameliorates HbA1c only partially as in UKPDS\textsuperscript{48}, whereas correcting glucose all throughout the day resulted in greater reduction of HbA1c as in DCCT\textsuperscript{84} and the Kumamoto study\textsuperscript{85}. The differences between the two studied group was 1\% in UKPDS and 2 \% in DCCT & Kumamoto.

These results pointed out that glucose levels in the post breakfast states are not merely a drift of fasting (prebreakfast) glucose but reflect the ability of the beta cells of the pancreas to mount an early phase (burst) of insulin secretion in response to food intake. Early insulin release is known to be impaired in the majority of diabetics and that bolus-basal (injection-basal) regimen is probably the best method to ensure optimal glycemic control.\textsuperscript{89-92}

We found HbA1c to be better correlated with fasting (r=0.601; P=0.000); similar to the result shown by Attbani (r =0.634; P less than 0.001).\textsuperscript{124} 3h postbreakfast glucose correlated well with HbA1c but less than that with the fasting glucose(r=0.547; p=0.000). Despite the strong correlation seen on single determination of blood glucose levels, HbA1c correlation to postprandial glucose mean levels is poor (r=0.202; p=0.102). This is hard to explain. It varies with results shown by Avington\textsuperscript{87} and Lerman\textsuperscript{88} and others.\textsuperscript{118-119} However it is in agreement with Bonora.\textsuperscript{120} It is also consisted with the conclusion reached by panel of experts designed by ADA to review the available data on postprandial glucose \textsuperscript{101} and goes with Unger statement.\textsuperscript{45}
On multivariate regression analyses all glucose parameters were independent predictors of glycated haemoglobin. The most constant was 3 h postbreakfast glucose which showed strong correlation when computed alone (P=0.00000), with fasting (P=0.000), with 2 hour (0.008) and when the three computed together only the 3h was significant (P=0.004).

Individually both fasting and 2h postprandial glucose showed significant power in prediction of HbA1c; (p =0.00; 0.043 respectively).

The correlation with 2 h postmeal was marginally significant. Possible explanation is that more hours are spent in the interprandial and nocturnal periods than in the postprandial phases; most Sudanese confine themselves to three meals. Consequently the average daily blood glucose, which is the main determinant of the extent of the glycation process, is a function more of interprandial and nocturnal glucose levels than of glucose spikes after meals.120

Data from the National Health and Nutrition Examination Survey Studies (NHANES) and IOEZ 125-127 based on medications targeting postprandial glucose in patients who weren't given basal medications yielded a reduction in postprandial glucose but didn’t substantially change HbA1c. However when the two regimens were given they resulted in lower value of HbA1c.102-103,125-127

Thus assessment of HbA1c is poorly informative of the degree of postprandial glucose content. However postprandial glucose demonstrated well the degree of poor control.
Recent studies have shown that postprandial glucose level might exert stronger deleterious effect on the cardiovascular system than does fasting glucose. This has been further substantiated by the fact that when glucose control aimed at normalizing fasting glucose alone, as in UKPDS, the effect on macroangiopathy was minimal.

Our finding that HbA1c is essentially dependant on FBG might explain the minimal effect of controlling HbA1c on CVD as in UKPDS or Veteran Administration Cooperative Study. Whereas targeting postprandial glucose, as in the Kumamoto or DIGAMI study had gained better cardiovascular outcome.

Furthermore, numerous observational studies had documented the increased risk of CVD associated with postprandial and/or post challenge glucose. Several experimental trials had supported the injurious effect of postprandial glucose on arterial wall and its proatherogenic properties.

More studies are awaited to clarify the subject; whether HbA1c suffices or postprandial should take the lead as a goal of therapy, at least to prevent CVD.

Comparing different glucose parameters& main clinical features with the type of treatment revealed that gender, duration of diabetes were major factors associated with the type of treatment but not the age or BMI, much in agreement with Bonora et al. Fasting blood glucose, HbA1c, 2 h post breakfast glucose, 3 h post breakfast glucose had shown significant correlations (P values, in order, were: 0.021, 0.021, 0.024, 0.035, 0.049).
The type of treatment showed marginal significance when correlated with 2 & 3 h; the relation with fasting, HbA1c and duration of diabetes was strongly significant. The latter pointed to the progressive nature of type 2 diabetes and stressed the insignificance of anthropometric measures like BMI in the evaluation of glycemic control. BMI tends to increase due to gain in weight exerted by most of medications used in diabetes especially sulphonylureas.

The fact that postprandial glucose levels were poorly correlated to the type of treatment given to the patient in contrast to fasting glucose and HbA1c (almost double P value) supports the innovation that the latter two are better correlated together and affect each other.

It also elucidates that they were not strongly related to post meal glucose levels and/or glucose excursion. It further strengthens the accumulating evidence that if postmeal glucose is not targeted on its own, its control would be poor and that specified drugs are needed for optimal glycemic control.

The relation between 2 h & 3 h postprandial glucose is close. Diet like drugs poorly controlled postprandial glucose which further strengthens the conclusion above.

Gender had a great impact on diabetes, female diabetics have poor prognosis. Females in all treatment groups were definitely overweight; with a mean BMI of 28 kg/m². They had the worst glycemic control despite the shorter duration of diabetes with a mean of 6.91 years compared to 11.41 in the male group.
The group using metformin and combined treatment had poorer glycemic control and more BMI values clearer in the male group; this could be explained by the late administration of these drugs in a group with prolonged duration of a progressive disease.

The controversy in correlation between single day readings of 2 hour glucose and the means of 3 readings corresponds with the simple fact that blood glucose levels vary day by day. Good evidence exists to support that several glucose determinations over a period of several weeks are better correlated to HbA1c than a single or few determinations in one day.\textsuperscript{112} The positivity of correlation on single determination with 2 hour postprandial glucose and lack of correlation with the average values may be explained, at least in part by that patients during study period had complied better with treatment and adhered closer to diet.

On average metabolic control was poor in most of the patients, this consisted with data shown by ElMahadi and others.\textsuperscript{44,123} Considerable proportion of patients, many of whom showing satisfactory HbA1c level, indeed had poor glycemic control after meals.

Because postprandial hyperglycemia is an independent risk factor for CVD in type 2 diabetes specific periodic assessment of postprandial glucose seems to be warranted along with FBG.

The significant position of 3hour post breakfast glucose signaled out in our study is an interesting finding .It could be extrapolated for 2 hours and/or fasting glucose in monitoring glycemic control. We suggested 140mg/dl as an upper limit. ADA recommended 140mg/dl level for the 2 hours postprandial.\textsuperscript{1}
Indeed diabetes type 2 is a progressive disease and glycemic control worsens over time. Nevertheless current guidelines and drugs used for treatment fail to achieve goals in most cases. Bolus-basal regimen is the best option available and should be adhered to. They mimic early and late rise of insulin. Oral bolus-basal regimen gives better control of both prandial and basal glucose. It delays the inevitable need for insulin. When insulin is needed in the management; bolus injection of rapid acting insulin is wiser and gives better diabetes control.

This modality of therapy neither restores the physiological functioning of B cells nor delivers insulin directly to the portal circulation where extensive hepatic clearance occurs then insulin is delivered into the peripheral circulation in a pulsatile fashion. The ideal drug which acts this way is still awaited.

**Conclusion**

The main results of the present study are that:

The majority of non-insulin treated type 2 diabetics in Sudan had higher than recommended blood glucose levels and exaggerated glucose excursion after meals. High postprandial glucose was often found when long term control and fasting glucose were satisfactory.

Three hour post breakfast glucose is strongly correlated to fasting, two hour and HbA1c.
two hour post breakfast glucose demonstrated poor correlation with the level of HbA1c.

In prediction of glycemic control both fasting and 3h postbreakfast glucose had showed to be sensitive in reflecting both good and poor control.

2hour postprandial glucose was found to be a poor predictor of good control but slightly more powerful than both fasting and three hour post breakfast in predicting poor glycemic control i.e HbA1c >8.5% .

BMI was a poor indicator of glycemic control. Multiple regression analysis showed no significant association between diabetic complications and the different parameters used to monitor glycemic control in the study.

Glucose monitoring in type 2 diabetes seems to be more complex than previously thought, because fasting blood glucose is a rather poor index of glucose levels throughout the day.

HbA1c seems to provide poor information on postprandial glucose levels and it provides no information on glucose excursion with meals in Sudanese patients.

Remarkable proportion of patients with type 2 diabetes showed poor glucose control in the postprandial period, even when HbA1c was satisfactory. They might benefit from medications specifically suited for providing more physiological control after meal ie oral (injection)-basal therapy.

Comprehensive management should entail monitoring not only FBG and/orHbA1c level but also glucose at other times especially in the postprandial period .2 hour postprandial glucose had been extensively studied, 3 hour postprandial glucose is an attractive option .
Patients shouldn’t be denied the test for postprandial glucose if show later than the précised 2 hours. 2-3 hours is a more flexible goal. More studies are awaited. Home glucose monitoring will make adherence easy.

In prevention of diabetic complications controlling postprandial hyperglycemia is at least as important as controlling fasting glycemia. Stricter control of postprandial glucose using specified drugs is likely to be useful in better control of glycemia and might result in better outcome in type 2diabetes.

The management of diabetic patients in Sudan is poor; adherence to guidelines lacked and intensive health education is needed.
Recommendations

- Comprehensive management of type 2 diabetes should entail monitoring not only fasting glucose and/or HbA1c levels but also glucose at other times especially in postprandial period.

- Patients shouldn’t be denied the test for post meal glucose if they show later than 2 hours. 2-3 hour postmeal glucose is a more flexible goal.

- Home glucose monitoring (SBGM) will make it easier to follow up glycemic control and would involve the patient in participating actively in his/her management.

- Intensive health education is direly needed in the field of diabetics care to address proper glycemic control, healthy lifestyle and control of high blood pressure & dyslipidemia.

- Training of medical personnel working in diabetic care centres and all health providing centres is needed for optimizing the management of diabetes; continuous medical education would be a necessity.

- Methods to recruit interventions for primary prevention of diabetes should be developed and implemented in the health system.

- The ideal treatment for patients with diabetes type 2 should include a combination of agents that lower basal plasma glucose and agents that control meal-related glucose excursions.

- More studies are awaited to further elucidate the value of two and three hour postprandial glucose in monitoring glycemia and the impact of postprandial glycemic control on morbidity & mortality in type 2 diabetes in Sudanese patients.
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