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Clinical and Biochemical Features of Adult Diabetes Mellitus in Sudan

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Abstract

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The high prevalence of diabetes mellitus among the Sudanese population is linked to obesity, poor glycaemic control and a high rate of complications. This study investigated 1/ Leptin hormone and its correlations with different biochemical characteristics in Sudanese diabetic subjects, 2/ The impact of glycaemic control on pregnancy outcome in pregnancies with diabetes, 3/ The glycaemic response to Sudanese traditional carbohydrate foods, 4/ The influence of glucose self-monitoring on the glycaemic control among this population, 5/ The health related quality of life in Sudanese subjects with diabetes-related lower limb amputation.

Leptin was significantly lower in diabetic subjects compared with controls of same BMI in both females ($P=0.0001$) and males ($P=0.019$). In diabetic subjects, serum leptin correlated positively with the homeostatic assessment (HOMA) of both beta-cell function ($P=0.018$) and insulin resistance ($P=0.038$). In controls, leptin correlated only with insulin resistance. Pregnancy complications were higher among diabetic compared with control women ($P<0.0001$) and varied with the type of diabetes. Infants of diabetic mothers had a higher incidence of neonatal complications than those of non-diabetic women ($P<0.0001$). In six Sudanese traditional carbohydrate meals over all differences in incremental AUCs were significant for both plasma glucose ($P=0.0092$) and insulin ($P=0.0001$). Millet porridge and wheat pancakes displayed significantly lower post-prandial glucose and insulin responses, whereas maize porridge induced a higher post-prandial glucose and insulin response. In type 2 diabetic subjects SMBG or SMUG was not related to glycaemic control. In type 1 diabetic subjects, SMBG was significantly associated with better glycaemic control, as assessed by HbA1c ($P=0.02$) and blood glucose at clinic visits ($P<0.0001$), similar associations were found for SMUG respectively. Neither glycaemic control nor glucose self-monitoring was associated with education level. Diabetic subjects with LLA had significantly poorer HRQL compared to a reference diabetic group ($P<0.0001$). Duration of diabetes and amputation had negative impact on HRQL in subjects with LLA ($P<0.0001$) respectively. Diabetic subjects with LLA had decreased sense of coherence and high presence of symptoms. Improving health services at the primary level is important to reduce the complications and burden of disease in the Sudanese population.

Keywords: diabetes mellitus, leptin, gestational diabetes mellitus, pregnancy, perinatal morbidity and mortality, carbohydrate rich-meals, self-monitoring, quality of life, sense of coherence, lower limb amputation, Sudan

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*To my mother and my father
To Sanaa and children
Ali, Ammar and Hamsa*

List of Papers

This thesis based on the following papers, which will be referred to in the text by their Roman Numerals:

- I Abdelgadir M, Elbagir M, Eltom M, Berne C, Ahren B. Reduced leptin concentrations in subjects with type 2 diabetes mellitus in Sudan. *Metabolism*. 2002 Mar;51(3):304-6.
- II Abdelgadir M, Elbagir M, Eltom A, Eltom M, Berne C. Factors affecting perinatal morbidity and mortality in pregnancies complicated by diabetes mellitus in Sudan. *Diabetes Res Clin Pract*. 2003 Apr;60(1):41-7.
- III Abdelgadir M, Abbas M, Jarvi A, Elbagir M, Eltom M, Berne C. Glycaemic and insulin responses of six traditional Sudanese carbohydrate-rich meals in subjects with Type 2 diabetes mellitus. *Diabet Med*. 2005 Feb;22(2):213-7.
- IV Abdelgadir M, Elbagir M, Eltom M, Berne C. The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan. *Diabetes Res Clin Pract* 2006. (In press)
- V Abdelgadir M, Shebeika W, Eltom M,, Berne C, Wikblad K. Health related quality of life and sense of coherence in Sudanese diabetic subjects with lower limb amputation. (Submitted)

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Abbreviations

DM – Diabetes Mellitus
CHD – Coronary Heart Disease
PVD – Peripheral Vascular Disease
DRCD – Diabetes Related Chronic Diseases
UKPDS – UK Prospective Diabetes Study
DCCT – Diabetes Control and Complication Trial Research Group
SMBG – Self-Monitoring of Blood Glucose
SMUG – Self-Monitoring of Urine Glucose
CGM – Continuous Glucose Monitoring
CSII – Continuous Subcutaneous Insulin Infusion
DNA – Deoxyribonucleic Acid
AP – Artificial Pancreas
HCHF – High Carbohydrate and High Fibre
GI – Glycaemic Index
CHD – Carbohydrate
ADA – American Diabetes Association
GL – Glycaemic Load
GCEs – Glycaemic Glucose Equivalents
DF – Dietary Fibre
GD – Gestational Diabetes
HRQL – Health Related Quality of Life
MOS – Medical Outcomes Study
SF – Short Form
DQOL – Diabetes Quality of Life
SOC – Sense of Coherence
LLA – Lower Limb Amputation
GQL – Gothenburg Quality of Life Instrument
AOAC – Association of Official Analytical Chemists
AACC – American Association of Cereal Chemists

Introduction

Brief historical overview

The earliest description of diabetes mellitus was found on 3rd Dynasty Egyptian papyrus (1552 BC) by physician Hesy-Ra, who mentioned polyuria (frequent urination) as a symptom. In the third century BC, Indian physicians in the Indian Sanskrit Susruta recorded the sweetness of the urine. The recent name of the disease (diabetes) appeared during the second century BC by Demetrios of Apamaia, a word that rooted from the Greek “diabeinein” which means siphon or to go to excess, where mellitus a Latin word stands for honeysweet had been added to the term later as result of the sweet-tasting urine. Aretaeus of Cappadocia drew the first clinical features of diabetes in the first century AD, increased urine volume, increased thirst and burning in the intestine. The 19th century was a century of the great discoveries in diabetes, Lancereaux and Lapierre distinguished between types of diabetes, diabetes with pancreatic origin (diabetes gras) and of non-pancreatic origin (diabetes maigre) and Langerhans discovered the link between pancreatic islet cells and diabetes. Many other scientists made serious impact in the field of diabetes such as Minkowski, Joseph von Mering and Banting.

Treatment of diabetes started with plant extracts in the ancient era and later limitation of dietary intake appeared to be useful especially for non-pancreatic diabetes. The discovery of insulin by Banting in early 1920s, the implication of sulphonylureas and other hypoglycaemic agents in the mid-forties and fifties played very significant roles in the management of diabetes.

Definition and classification of diabetes mellitus

According to the World Health Organization (WHO; 1980 and revised 1985, 1999) T diabetes mellitus is defined as a metabolic disorder of multiple aetiologies characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. (Table 1 and 2 show the diagnostic and classification criteria for DM).

Table 1. *Diagnostic criteria for diabetes mellitus*

	Glucose concentration (mmol/L)		
	Whole blood		Plasma
	Venous	Capillary	Venous
Diabetes Mellitus			
Fasting*	≥6.1	≥6.1	≥7.0
2 h after 75 oral glucose load	≥10.0	≥11.1	≥11.1

Table 2. *Classification of diabetes mellitus*

Type 1 diabetes (beta-cell destruction, usually leading to absolute insulin deficiency)

Autoimmune

Idiopathic

Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)

Other specific types

Genetic defects of beta-cell function

Genetic defects in insulin action

Diseases of the exocrine pancreas

Endocrinopathies

Drug- or chemical-induced

Infections

Uncommon forms of immune-mediated diabetes

Other genetic syndromes sometimes associated with diabetes

Gestational diabetes

Global epidemiology of diabetes mellitus

Due to aging, accelerated population growth, urbanization and high prevalence of obesity and an inactive lifestyle, the number of people with diabetes is increasing globally at a rapid speed. Important differences have been reported in the occurrence of DM and its complications between countries and between ethnic, cultural and even age groups within the same country. The prevalence of DM worldwide was estimated at 4% in 1995 and is expected to rise to 5.4% by the year 2025 [4]. Consequently, the number of adults with DM will rise from 139 million to 300 million by the year 2025. The major part of this increase will occur in developing countries. There will be a 170% increase, from 84 to 128 million, in developing countries, and a 42% increase from 51 to 72 million in the developed countries.

According to WHO estimates in 2000 the burden of diabetes is massive globally, with 20-35% of the diabetic patients suffering from neuropathy, 30-45% with retinopathy, 10-20% with nephropathy, and from 10 to 25% having cardiovascular disease [5]. Thus, the effect of diabetes on mortality and morbidity, its rapidly growing prevalence, and the high economic and human cost give emphasis on diabetes as a major global public health problem [6,7,8].

Diabetes mellitus in Africa

In Africa, at the start of the past century, DM was seen as a rare medical condition. Albert Cook, a medical missionary, in stated in 1901 that “diabetes is rather uncommon and very fatal...” [9]. Since the early 1960s a number of epidemiological studies has been carried out to elucidate the prevalence and nature of diabetes in the African population. The prevalence of DM in Africa is following the international trends. High prevalence and incidence of the disease are expected [4] in parallel to the decrease in fertility and infectious diseases, the increase in non-communicable diseases, life expectancy and changes in lifestyle [10].

The majority of people in Africa with diabetes is between 45 and 64 year of age. African diabetic patients are to 70-90% composed by type 2 diabetes and 25% type 1 diabetes [11,12]. The prevalence of type 2 DM in the adult population ranges from 0% in Togo to 10.4% in Northern Sudan, and the prevalence of type 1 DM in all ages ranges from 0.3/1000 in Nigeria to 0.95/1000 in Sudan [13], Figure 1.

DM in Africa is more often taking a severe course and shows high rates of acute and chronic complications and a poor outcome [10].

The burden of diabetes cost in Africa is huge and depending upon the individual and the family. Although this field of diabetes suffer from paucity of information, it has been shown in a study by Cameroon that 50% of diabe-

tes care is paid by the patients, 44% by the family, 2% by the employer, 2% charities and others, and only 2% by the government [14].

This difficulty of providing free national health services for patients with diabetes in Africa, and the overall failure to deliver and maintain health care, is shared by almost all African countries as shown in the WHO health report 2000, ranking 80% of African countries to the fourth and fifth quintiles according to the overall performance of their health systems [15]. Thus, recommendations founded on the results of the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complication Trial Research Group (DCCT) showing benefits on intensive glycaemic control [16,17], and development of models and tools for diabetes health care in Africa, could potentially result in a substantial decrease in diabetes complications in this population [18,19].

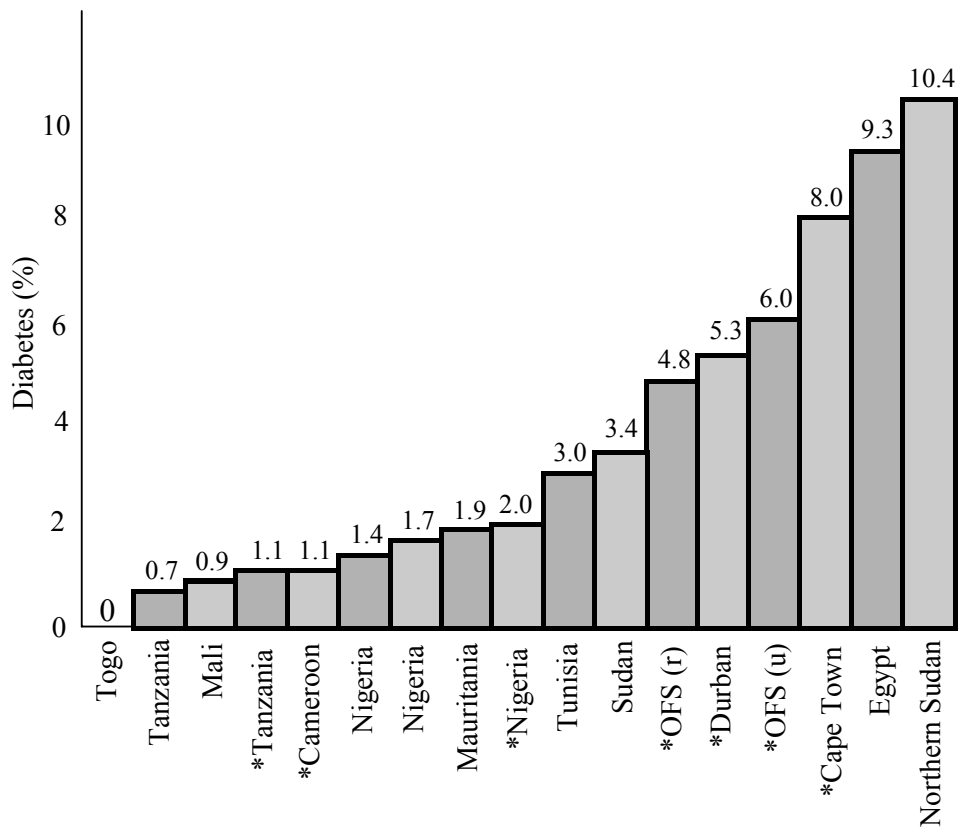


Figure 1. Prevalence of diabetes mellitus in Africa.

*Age adjusted, (r) rural, (u) urban

Modified after Ayesha A et al, J Cardiovasc Risk 2003,10:77-83

Diabetes mellitus in Sudan

General overview



Figure 2. Map of the Sudan
Source: CIA world fact book at <http://www.cia.gov/>

Sudan is the largest country in Africa occupying a territory of 2.5 million square kilometres. The geographical diversity of Sudan has had a direct impact upon economic, social, political, and cultural life in modern Sudan with its multifarious ethnic and cultural composition. The distinct culture of Sudan is regarded as the oldest in Sub-Saharan Africa. Sudan has had contacts with Middle East and Mediterranean civilizations since ancient times. The western parts have many contacts with West Africa, and the eastern parts have maintained close links with the countries at the Indian Ocean. The population in the north-eastern parts of the country has undergone an ethnic absorption of immigrant Arabs during times of Islamisation, and culturally

becoming Arabised. This process has been extended deep into the Central and Western parts, but with much less influence on the population in the Western parts.

Internal migration has taken place in different parts of Sudan from rural areas and small towns to big cities, particularly to the capital Khartoum. This has been complicated by displacement of large proportion of populations from draught and famine prone area and war torn areas in the western and southern parts of the country. [20]

The total population is about 34 million, with 70% in the northern parts. 37% of the population are urban settlers and 10% of the rural inhabitants are nomads.

The annual growth rate of the population is 2.7%, and the average size of households is 5.8 persons. The population pyramid is characteristic of a low-income country with 44% of the population below 15 years and 2.3% over 65 years of age. Infant mortality rate is reportedly 65/1.000 live births and the maternal mortality ratio 590 death/100.000 live births. The income per capita is 858.000 SP/year (330 USD). Staple foods are sorghum, millet, wheat and maize.

Diabetes mellitus in Sudan

The prevalence of DM in the Sudan, as in many other low-income countries, is increasing to epidemic proportions, leading to the emergence of a public health problem of major socio-economic impact. Before 1989 all knowledge about DM in the Sudanese population was based on a few hospital-based studies, but later a series of investigations explored epidemiology and characteristics of the disease in collaboration with Uppsala University, Sweden.

Recent information indicates that type 2 DM is common among the adult population of northern Sudan. The prevalence is estimated to be 3.4% over 25 year of age. It was found to be 5.5% in the Northern State and 8.6% in Khartoum State and lowest in the western desert-like parts, 0.9% [21]. The prevalence was higher in a certain communities in the Northern State, particularly the Danagla tribe where it reached 10.4%. However, no significant urban/rural difference was observed [22].

Prevalence of type 1 DM was estimated at 0.1 % among school children 7-14 years of age [23]. The natural history of DM in the Sudanese population is strongly linked to obesity, approximately 75% of the diabetic patients have type 2 diabetes, and 40% of them were obese and have a family history of diabetes [24]. DM in this population often had a poor glycaemic control, with a high prevalence of acute and chronic complications and a low quality of life [25-28]. Due to limited resources, most of the patients (51%) had reduced or abandoned insulin therapy due to non-availability or non-affordability of this drug. Most patients did not receive a satisfactory diabe-

tes care and education, leading to lower rate of clinic attendance (55%), and dietary non-compliance (78.5%) [29].

In Sudan, a public health approach should be the cornerstone in providing an acceptable diabetes care. The formulation of a national diabetes management program is needed – with an objective also of working towards prevention of this rapidly increasing disease. Further, public health education is needed regarding the symptoms of the disease and risk factors for its development, so that those who have the disease can present early.

Community-based programmes for optimal diabetes management should be based on diabetes centres, which should be an integral part of the health care delivery system from the primary care at the local governmental level, to the tertiary centres for the management of the most serious complications. Social support is essential to reduce social and psychological problems, often present in patients and their relatives, in order to cope with the burden of diabetes, its treatment and social consequences. A few studies have been carried out in Sudan focused on DM risk factors such as obesity and glycaemic control [30,31]. However, the knowledge base is still weak, and financial resources are needed for research as well as for prevention and management of diabetes in Africa.

Complications of diabetes mellitus

For both type 1 and type 2 diabetes, clinical course and prognosis of the disease are linked to the glycaemic control and duration of diabetes [32]. Macrovascular diseases caused by diabetes are the predominant causes of mortality and morbidity in diabetes [33], including coronary heart disease (CHD), peripheral vascular disease (PVD) and cerebrovascular disease [34]. Microvascular complications of diabetes consist of neuropathy, retinopathy and nephropathy. Limb amputations, infections and ulceration are common complications of diabetes that could be prevented through foot care programs. [35]. Acute metabolic complications include diabetic ketoacidosis, hypoglycemia and hyperosmolar non-ketotic coma.

Prevention of diabetes mellitus and its complications

A number of classic models for DM health care in the community were presented previously [36]. However, it is now well known that any chosen diabetic care approach should maintain tight glycaemic control, which in turn decreases complications and improves the outcome of type 1 as well as type 2 DM [16,37,38]. Therefore, a population strategy to reduce the prevalence and consequence of DM and Diabetes Related Chronic Diseases (DRCD), should include first identification of DM cases from a high risk group

(screening), second, to establish appropriate management of DM and DRCD patients (management) and, thirdly, to modify risk factors in order to prevent diabetes in those being most at risk.

Since DM is a disease of long duration requiring long-term treatment the health service provider should develop an appropriate model for management at primary, secondary and tertiary levels as part of a public health approach. These activities or models must include not only clinical services, but also educational programs for families and community lay people with active participation of the diabetic patients themselves.

Diabetes mellitus cost

Diabetes represents a heavy burden for communities and individuals in particular, carrying high direct and indirect costs [39]. The direct costs are related to health care costs of detection, treatment, prevention and rehabilitation. This includes hospitalization, outpatient visits and cost of travelling to diabetes clinics, medication supplies such as insulin, syringes, tablets, blood and urine monitoring equipment. The indirect costs are linked to loss of productivity due to premature death, short-term illness and permanent disability.

Different studies have been performed all over the world estimating costs of diabetes. It has been shown that diabetic patients generally have 2-3 times higher health care costs than non-diabetics [40].

Estimates of diabetes costs are important and may provide information to prioritise resource allocation, attract additional resource and manage available assets for diabetes care.

Diabetes mellitus control

Self-monitoring of blood glucose (SMBG)

Self-monitoring of blood glucose has become of prime importance in management of both type 1 and type 2 diabetic patients [41-43]. Different types of glucose meters have been used with varying accuracy and precision [44-46].

Two different technologies are used for self-monitoring devices (glucometers), electrochemical sensors based on electrochemical reactions, they could be coulometric or amperometric, both employ an electrochemical reaction where an electrical charge is generated by ionic exchange involved in the reaction. The photometric colour reflectance- that assumed to be older-based on visible change of reagent colour when exposed to blood glucose concentration or urine, reflectance spectrometer conveys and displays the colour change into figures on a screen.

The cost of SMBG is a matter of concern, even among patients in high-income countries [47], resulting in decreased frequency of monitoring [48].

Continuous glucose monitoring (CGM), advances in diabetes care

Most recently, new technologies have been established to potentially improve diabetes management and outcome. Important advances were made in insulin delivery systems such as continuous subcutaneous insulin infusion (CSII) also known as insulin pumps and aerosolised insulin delivery using inhalers, besides, using recombinant DNA technology to produce human insulin analogues and trials of introducing an artificial pancreas (AP), which is expected within the next 5 years [49]. However, as SMBG is considered the most valuable advance since the discovery of insulin in 1921. The appearance of continuous glucose monitoring and the new monitoring systems adds to the management tools, revealing fluctuations in glucose levels day and night, detecting nocturnal asymptomatic hypoglycaemia or other problems in blood glucose control. However, the major obstacle in CGM and other advances is the high cost [50,51].

Dietary control

The importance of nutritional recommendations for subjects with diabetes has been known as major issue in treatment of the disease. The target of dietary recommendations is prevention and treatment of diabetes through improving glycaemic control and lipid profile and optimizing the blood pressure, as high risk of microvascular abnormalities and cardiovascular diseases in diabetic subjects is linked to increased postprandial glucose response [52,53].

For the diabetic patients adhering to dietary recommendation is not an easy task as dietary patterns differ greatly, but consumption of high carbohydrate and high fibre (HCHF) diets has been agreed to be essential [54]. After the appearance and development of the glycaemic index concept (GI) [55-57], the recent ADA dietary recommendation indicated to use glycaemic index/glycaemic load (GI/GL) in choice of carbohydrate foods, where those with low GI are preferred for people with diabetes [58]. New concepts dealing with the total glycaemic response of carbohydrate foods such as the glycaemic load concept (GL) and glycaemic glucose equivalents (GCEs) are now also available [59,60]. However, in a low-income setting the consumption of traditional carbohydrate foods which are slowly digested with high dietary fibre (DF) content considered to delay the onset of the diabetes and improve the glycaemic control [61,62].

Diabetes mellitus control in pregnancy

Several chronic medical diseases were found to associate pregnancy, but diabetes considered the most prevalent among them accounting for 0.2 to 0.5% of all births [63]. Gestational diabetes (GD) occurs in 3-5% of pregnant women, it has the same adverse effect on maternal and neonatal outcome as type 1 and 2 diabetes with pregnancy if normoglycaemia was not maintained [64].

Gestational diabetes prevalence was also found to be linked to the prevalence of type 2 diabetes in a given population and could increase if risk factors were not taken in consideration such as high maternal age and parity, previous obstetric outcome of macrosomic infants and family history of diabetes [64]. However, maternal hyperglycaemia have been recognized to be the main cause of perinatal morbidity and mortality as well as the congenital malformation [65,66]. The high perinatal morbidity and mortality during diabetic pregnancies could significantly decrease if glycaemic control improved [67,68]. It is important to point that better outcome of pregnancy complicated by diabetes mellitus has been achieved in high-income countries where, this improved outcome is not clearly observed in low-income countries as the perinatal morbidity and mortality is still high.

Diabetes mellitus and obesity

Rates of type 2 diabetes have increased within the last decades. This is due largely to the global epidemic of obesity, a major risk factor for developing type 2 diabetes. Development of obesity is related mainly to decreased physical activity and increased caloric intake, besides genetic background which determines the tendency to obesity [69]. Prevalence rates for overweight and obese people vary according to region, but obesity now associated with poverty even in low-income countries and burden of disease worldwide, and this turns obesity issue in a matter of concern for World Health Organization (WHO) and urges it to issue consensus definition of different degrees of overweight and obesity in adults in 2000 [70] table 3.

Table 3. WHO classification of obesity in terms of BMI (kg/m^2)

Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5-24.9	Average
Overweight	≥ 25	
Pre-obese	25.0-19.9	Increases
Obese class 1	30.0-34.9	Moderate
Obese class 2	35.0-39.9	Severe
Obese class 3	≥ 40.0	Very severe

Waist circumference		
	Women	Men
Above action level 1	≥ 80 cm	≥ 94 cm
Above action level 2	≥ 88 cm	≥ 102 cm

As obesity resulted due to accumulation of adipose tissue to excess that by time affects negatively both physical and psychological health and well-being, it has been found that adipose tissues produce a variety of adipocytokines which appeared to play a key role in the development and progression of the disease, including leptin, resistin, adiponectin, tumor necrosis factor and adiponectin [71].

Leptin is a 167-amino acid protein with a molecular mass of 16 kDa produced by the *ob* gene that has been recently discovered, its name rooted from the Greek word (leptos) meaning thin and proposed to be an important regulator of body weight and adipose mass [72]. Leptin is produced mainly by mature adipocytes, although production in minor extents from other tissues such as placenta, fundus of the stomach, skeletal muscle and liver has been reported [73].

Leptin concentrations were found to correlate with insulin, insulin resistance, glucose and measures of adiposity [74] with marked sexual dimorphism as females have higher leptin concentrations than males [75].

Regulation mechanism of leptin proposed to be multifactorial, involvements of genetic factors, glucocorticosteroids, catecholamines, body fat distribution and insulin have been shown in different studies [76-80]. Leptin acts centrally on the hypothalamus nuclei through regulation of the hypothalamic neuropeptides, repressing the expression of orexigenic peptides and inducing anorexigenic peptides resulting in inhibition of appetite and food intake, reduction of body weight and increasing energy expenditure [81-83].

Diabetes mellitus and health related quality of life (HRQL)

Maintaining satisfactory glycaemic control is the main objective in diabetes management, as better diabetes control found to reduce mortality and morbidity rates significantly among diabetic patients but with fairly high socioeconomic cost. The over all burden of the disease has an adverse impact on diabetic patient's quality of life and well-being, therefore improving quality of life and well-being of the diabetic people turn to be an increasing demand to achieve better diabetes management.

The psychological load of living with diabetes affects self-efficacy, self-care behaviour, long term glycaemic control and complications and also quality of life [84].

Quality of life measurements include perceived physical and mental well-being and physical and social functioning. Each domain used to evaluate health related quality of life (HRQL) could be an independent determinant, therefore creating a multidimensional assessment to quality of life was mandatory [85]. Different instruments were suggested to measure HRQL in diabetic people; those instruments are generic or disease specific [86]. The Medical Outcomes Study (MOS) Short Form General Health Survey is the most used generic instrument with its different forms (SF-36, SF-20, SF-12)[87-89]. It includes physical and mental health measures covering many positive and negative health conditions that conceptualize physical, mental and social functioning, well-being and general health perception and satisfaction [85] Another often used disease specific instrument measuring diabetes-specific quality of life is the Diabetes Quality of Life (DQOL) measure from the Diabetes Control and Complications Trial (DCCT) [90]. This instrument is designed to measure effect and satisfaction of diabetes treatment, worries about future impact of diabetes and social matters and overall well-being.

Patient's perception of quality of life in different studies was found to be affected by duration of diabetes, glycaemic control, and presence of diabetes complications, age, education, gender and socio-economic status [91-95]. The quality of life of an individual is multifaceted and a patient's coping capacity was found to be an important determinant of HRQL [96-97]. The sense of coherence (SOC) [96] is considered to be a valuable tool in assessing coping capacity. Sense of coherence theory proposed that people who score high on SOC are highly capable of solving cognitive problems. High degree of acceptance of diabetes and good self-perceived health was linked to a high SOC score, and indirectly to a better quality of life among people with diabetes [98,99].

Aims of the study

The main aim of the present studies is to explore different clinical and biochemical aspects of diabetes in relation to glycaemia and glucose homeostasis with the course of diabetes mellitus in the Sudan and to identify possible factors that might improve diabetes care among this population.

Main objectives

To investigate the possible association of leptin and different clinical and biochemical characteristics of diabetes among Sudanese subjects.

To investigate the influence of maternal metabolic control on perinatal morbidity and mortality in Sudanese pregnant diabetic women.

To study the glycaemic response of Sudanese traditional carbohydrate-rich meals in Sudanese subjects with diabetes.

To investigate the influence of self-monitoring of glucose on the glycaemic control in Sudanese diabetic subjects.

To investigate the influence of diabetes-related lower limb amputation on health related quality of life in Sudanese diabetic subjects.

Subjects and methods

Subjects were recruited from outpatient diabetes clinic at Omdurman Teaching Hospital, study (I), (III), (IV) and (V) and from the antenatal care clinic of Omdurman Maternity Hospital, study (II).

Paper (I)

One hundred and four diabetic patients (males/females, 45/59) were recruited from the outpatient diabetes clinic at Omdurman Teaching Hospital. They were treated with glibenclamide (n=80), gliclazide (n=1), metformin (n=4) and diet alone (n=19). An age and BMI-matched group of 75 (males/females, 41/34) apparently healthy non-diabetic subjects, who live in the same area, served as controls.

Paper (II)

Eighty-eight diabetic pregnant women who visited the clinic for their regular follow-up were included consecutively in the study. Of these women, 38 had type 1 diabetes mellitus and 31 had type 2 diabetes (n=17 treated by diet, n=14 by insulin). Gestational diabetes was diagnosed in 19 women (n=11 treated by diet, n=8 by insulin). 50 healthy pregnant women, matched for age, body mass index and parity, were selected to act as a reference group.

Paper (III)

Ten apparently healthy patients with type 2 diabetes mellitus (males/females, 6/4) were recruited from the outpatient diabetes clinic at Omdurman Teaching Hospital. Four patients were treated with diet alone and six also received glibenclamide

Paper (IV)

A group of 193 consecutive type 2 and type 1 diabetic subjects (95 men, 98 women) from the outpatient diabetes clinic at Omdurman Teaching Hospital were studied.

Paper (V)

A total of 60 (males/females, 40/20) diabetic subjects with lower limb amputation (LLA) and 60 (males/females, 23/37) apparently healthy diabetic reference subjects from diabetes clinic at Omdurman Teaching Hospital were studied.

Methods

A questionnaire including personal details and clinical characteristics was completed for all subjects, Blood pressure, weight and height were measured and body mass index (BMI) was calculated. In paper (I) the fasting state blood samples were drawn for the determination of serum leptin, glucose, insulin and proinsulin.

In paper (II) venous whole blood from all patients was drawn in EDTA-containing tubes for determination of HbA_{1C} at interview, and at delivery and another sample was centrifuged for the measurement of C-peptide and a sample from the umbilical cord to measure C-peptide in newborns.

In paper (III) blood samples were collected in the fasting state before each meal and at 30, 60, 120, 240 minutes after the start of the meal for determination of plasma glucose and plasma insulin.

In paper (IV) fasting blood glucose was measured in 104 subjects with type 2 diabetes using a glucose meter and blood was obtained for serum glucose measurement in the laboratory. In the remaining 89 diabetic subjects random blood glucose was measured using the same glucose meter and a whole blood sample was drawn for laboratory assessment of HbA_{1c}. Data on self-monitoring and other clinical and personal characteristics were recorded.

In paper (V) in both diabetic subjects with lower limb amputation and reference healthy diabetic subjects health-related quality of life (HRQL) was measured using The Medical Outcomes Study questionnaire (MOS). For the diabetic subjects with LLA, the questionnaire included also Antonovsky Sense of Coherence scale (SOC-13) and a symptom check list from the Gothenburg Quality of Life Instrument (GQL).

Chemical analysis

Leptin was measured using RIA kit (Linko Research, St. Charles, MO, USA), detecting immunoreactive human leptin with sensitivity 0,5 ng/mL. Insulin was measured with specific RIA cross-reacting with less than 0.2% proinsulin (Linko Research, St. Charles, MO, USA). Total serum proinsulin levels were measured using a goat antibody raised against human proinsulin, human proinsulin standards and ¹²⁵I-human proinsulin as tracer (Linko Res. Inc.). Serum glucose was analyzed using the glucose oxidase technique.

HbA_{1C} was determined by High Performance Liquid Chromatography (reference range 3.5-5.0%). Serum C-peptide concentration was by radio-immunoassay (detection limit 0.05 nmol/L).

In paper (III) the proximate chemical composition of the flour and the meals was measured as, moisture and ash according to recommendations of AOAC, fat and protein using the Kjeltec system, crude fibre according to recommendation methods of AACC, and carbohydrate calculated by differences.

Statistical analysis

All data were expressed as mean \pm SD. Student's test or its non-parametric version and χ^2 test were used where relevant for comparison between groups for variables with normal or log-normal distribution. Adjustment calculated as Pearson's partial correlation coefficients. Analysis of variance model with factors was used where relevant.

Homeostasis model assessment (HOMA) was used to assess pancreatic β -cell function (HOMA B) and insulin resistance (HOMA IR) using fasting insulin and glucose concentrations by the formula: HOMA-B (%) = $20 \times [\text{insulin}]/(\text{glucose} - 3,5)$ and HOMA-IR = $\text{insulin}/(22,5e^{-\ln[\text{glucose}]})$ in paper (I).

Area under the curve (AUC) was calculated according to the trapezoidal model in paper (II).

Results and discussion

Paper (I)

Leptin was higher in females than in males and correlated significantly to BMI. The main novel finding was that serum leptin was significantly lower in diabetic subjects compared to controls in both females ($P=0.0001$) and males ($P=0.019$) although BMI did not differ between diabetic and non-diabetic subjects. Diabetic subjects treated with sulphonylurea ($n=81$) had lower BMI than those treated with diet alone or other hypoglycemic drugs ($n=23$) ($P=0.0017$), but there was no difference in leptin levels between the two groups after adjustment for BMI ($P=0.87$). In diabetic subjects serum leptin correlated positively with the homeostatic assessment (HOMA) of both β -cell function ($P=0.018$) and insulin resistance ($P=0.038$), whereas in control subjects, leptin correlated with insulin resistance ($P=0.0016$) but not to β -cell function. Diabetic subjects had higher proinsulin levels ($P=0.0031$) and higher proinsulin to insulin ratio ($P=0.0003$) than non-diabetic subjects. In univariate analysis, proinsulin in diabetic subjects showed a weak correlation to leptin ($P=0.049$).

The main novel finding in this study was that the Sudanese subjects with type 2 diabetes had lower leptin levels than the controls. A possible explanation for the lower leptin levels in diabetic subjects is a difference in the fat distribution between the two groups, another possibility, however, is a relative insulin deficiency in the diabetic subjects, because insulin is an important stimulator of leptin production.

Paper (II)

The mean fasting blood glucose was 11.1 ± 2.8 mmol/L and the mean HbA_{1C} at interview was 8.8 ± 2.1 % in the diabetic women. Pregnancy complications such as Caesarean sections, urinary tract infections, pregnancy induced hypertension and intrauterine foetal death, were higher among diabetic women compared to controls ($P<0.0001$) and varied with the type of diabetes. Infants of diabetic mothers had a higher incidence of neonatal complications than those of non-diabetic women (54.4% vs. 20.0%; $P<0.0001$). Infants without complications and who were born to diabetic mothers had better

Apgar scores at 5 minutes (9.8 ± 0.5 vs. 8.9 ± 1.6 ; $P < 0.01$) and lower cord C-peptide when compared to infants with complications ($P < 0.05$).

The nature and distribution of the complications associated with maternal diabetes were found not only to be linked to the degree of hyperglycaemia, but also to the type of diabetes, they were more frequent in type 1 DM followed by type 2 DM and less in gestational diabetes. Hyperinsulinaemia in the infants of the diabetic mothers is related to the major complications that occurred to those infants. Maternal hyperglycaemia is the main factor influencing not only maternal wellbeing, but also foetal and neonatal morbidity and mortality.

Paper (III)

Proximate analysis of wet samples of different meals is shown in Table 4. A significant variation in AUC for glucose and insulin responses were found between meals, the over all differences in incremental AUC:s between the six meals were significant for both plasma glucose ($P = 0.0092$) and insulin ($P = 0.0001$). The 2 hours glucose values were 10.5 ± 2.7 for sorghum flatbread, 9.5 ± 3.1 sorghum porridge, 10.3 ± 3.4 millet flatbread, 10.6 ± 3.6 millet porridge, 11.4 ± 2.7 maize porridge and 8.7 ± 2.4 for the wheat pancakes. The comparison between the AUC:s of the meals showed that millet acida (porridge) followed by wheat gorasa (pancakes) displayed significantly lower postprandial glucose and insulin responses, whereas maize acida induced a higher postprandial glucose and insulin response.

The findings put emphasis on the importance of the glycaemic concept in choice of diets of desirable glycaemic responses and thus provide a guide to select meals with low postprandial glucose elevation for diabetic subjects residing in low-income countries. A better compliance to traditional diets with higher fibre content could be a simple and cheap way for diabetic subjects to decrease postprandial glucose, hyperinsulinaemia and hypertriglyceridaemia.

Table 4. Proximate analysis. Wet sample carbohydrate foods percent (%) per/100 gms

Item	Moisture	CHO	Protein	Fat	Ash	Crude Fibre
Kisra sorghum	45.06	44.76	7.78	0.67	0.90	0.83
Acida sorghum	80.12	13.47	3.16	0.40	0.48	0.37
Kisra millet	43.02	43.69	9.18	2.0	1.32	0.79
Acida millet	73.46	20.52	4.30	0.63	0.63	0.46
Acida maize	81.74	14.40	2.56	0.58	0.44	0.28
Gorasa wheat	53.34	38.02	5.70	0.41	1.57	0.96
Waika	92.00	3.98	1.11	0.76	1.93	0.55

Paper (IV)

There was a significant correlation between blood glucose values measured with the glucose meter and values determined in the laboratory ($r=0.77$; $P=0.0001$).

The frequency of self-monitoring of blood glucose (SMBG) and self-monitoring of urine glucose (SMUG) related to the mean blood glucose are shown in Table 5.

The glycaemic control in the type 2 diabetic subjects did not differ significantly by frequency of SMBG or SMUG when assessed as HbA1c. Patients who practiced SMUG daily had HbA1c $7.2\pm 1.2\%$, once weekly $7.6\pm 1.9\%$ or never $9.3\pm 2.3\%$. Those who practised SMBG weekly had HbA1c $9.1\pm 2.2\%$ and never $7.1\pm 1.9\%$. A similar finding was observed in type 2 diabetic subjects assessed by fasting serum glucose.

Also the patients' level of education appeared to be unrelated to glycaemic control, measured by fasting serum glucose, in subjects with type 2 diabetes. Those who had no education had 8.1 ± 4.3 mmol/l as compared to 9.1 ± 5.0 mmol/l among those with primary education, 7.8 ± 3.6 mmol/l among those with secondary education and 8.9 ± 3.8 mmol/l when having university education. Further, education was not related to frequency of SMUG. The same observation was made in type 2 diabetes subjects assessed by HbA1c. Education was not found to correlate with either glycaemic control or patterns of both SMBG and SMUG.

Eighty four percent of subjects with type 1 diabetes ($n=42$) never performed SMUG, 14% ($n=7$) did so once a week and only 2% ($n=1$) once daily. Eighty percent did not perform SMUG ($n=40$), while 10% did so once per week ($n=5$) and 10% ($n=5$) once daily. Type 1 diabetic subjects, who never monitored blood glucose, had significantly higher random blood glucose than those who did (17.2 ± 4.5 mmol/l vs. 7.2 ± 1.8 mmol/l, $P=<0.0001$), and higher HbA1c ($9.4\pm 2.1\%$ vs. $5.6\pm 1.5\%$, $P=0.02$). Type 1 diabetic patients who never monitored urine glucose had also significantly increased random glucose levels compared to those who did at least once weekly (17.2 ± 4.8 mmol/l vs. 8.3 ± 2.3 mmol/l, $P=0.02$), and higher HbA1c ($9.4\pm 2.2\%$ vs. $6.7\pm 1.3\%$, $P=0.04$).

Similarly, there was no significant association between education and HbA1c in type 1 diabetic subjects; $9.2\pm 3.1\%$, $8.6\pm 2.0\%$, $8.9\pm 2.4\%$, and $9.7\pm 2.0\%$ for no education, primary, secondary and university education, respectively, Figure.3 Education in the type 1 diabetic patients was not associated with the frequency of SMUG.

In an urban diabetic population in Sudan the frequency of self-monitoring of glucose (blood or urine) was found to be positively associated to good glycaemic control in type 1 diabetes but not in type 2 diabetes patients. Education level of the patients was neither associated to frequency of self-monitoring nor to level of glycaemic control.

Table 5. Frequency distribution of SMBG and SMUG related to blood glucose.

Self-monitoring technique	SMBG	SMUG
	Blood glucose (mmol/l)	
Once a day	6.2± 1.8 (n=4)	7.4± 2.9 (n=7)
Once a week	9.4± 3.5 (n=48)	10.5± 3.5 (n=33)
None	13.1± 4.5 (n=141)	13.4± 4.5 (n=153)

Mean ± SD

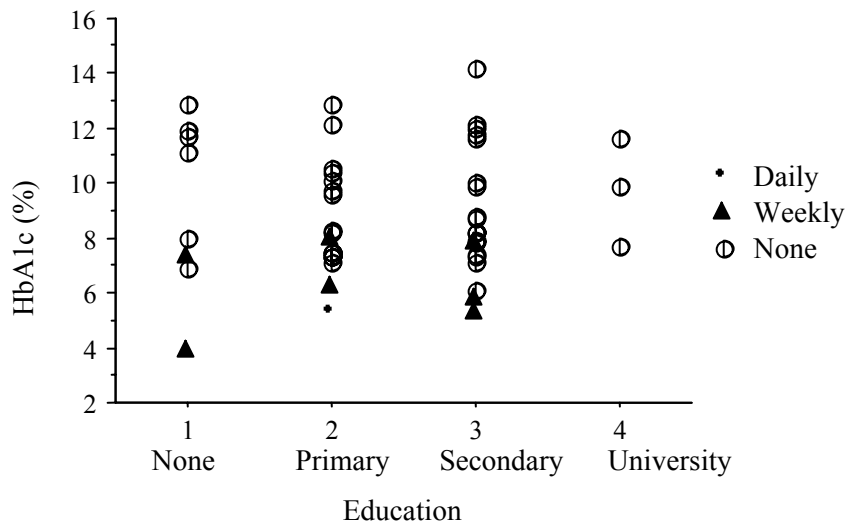


Figure 3. Blood glucose monitoring and HbA1c values. Results given for different levels of blood self-monitoring. Type 1 diabetes patients.

Paper (V)

No differences were found in education when comparing the two groups ($P=0.26$) but subjects in the reference group were significantly younger and had shorter duration of diabetes. Among diabetic subjects with LLA, 44 (73.3%) had below knee amputation and 16 above knee amputation. Forty-four of the diabetic subjects with LLA had a history of previous LL amputations. Twenty-eight (46.7%) rated their average blood glucose in the range (10 – 16,7 mmol/l), while 5 (8.3%) had average blood >16,7 mmol/l during the last 6 months.

Subjects with LLA had significantly poorer HRQL in all domains except for family satisfaction and positive feelings. In subjects with LLA no significant differences were found between males and females except for role physical for which females had a slightly better score than males ($P=0.04$) and also better sleep was reported for females ($P=0.002$). The same comparison between genders in the reference group was non-significant for all variables. Duration of diabetes in subjects with LLA did not correlate with either physical functioning or role physical, but it showed significant negative correlation with all other HRQL domains ($P=<0.0001$). It was also found that the time since amputation was negatively linked to HRQL ($P=<0.0001$). In reference subjects duration of diabetes showed a significantly negative correlation with all HRQL domains ($P=<0.0001$).

Among the diabetic subjects with LLA the mean SOC was 52.6 ± 8.6 . Sense of Coherence in this group showed negative correlation with both duration of amputation and duration of diabetes ($P=<0.0001$) respectively, but positive correlation with the overall HRQL ($P=<0.0001$). SOC did not differ between males and females of the group (53.1 ± 8.4 vs. 52.0 ± 9.3 , $P=0.61$). Also SOC in subjects with LLA did not correlate either to negative feelings ($P=0.46$) or to role emotional ($P=0.07$). On the other hand it correlated significantly negative with physical functioning and role physical, and showed a significant positive correlation with positive feelings, family satisfaction and sleep ($P=<0.0001$) respectively. SOC among this group was found to be positively linked to age ($P=0.005$). Also SOC was higher among those who followed information about foot care compared to others who did not (54.7 ± 8.2 vs. 47.8 ± 7.8 , $P=0.004$).

The prevalence of symptoms in the LLA group ranged between 0% for irritability to 76.7% for visual impairment. Other symptoms with high prevalence among this group were general fatigue (50%), nervousness and sweating (53.3%) and depression, joint and leg pain (31.7%) respectively. In subjects with LLA the symptoms correlated positively with both duration of diabetes and duration of amputation, and negatively with SOC ($P=<0.0001$). Presence of symptoms also correlated negatively to HRQL domains in particular negative feelings, positive feelings, family satisfaction, sleep

($P < 0.0001$), and role emotional ($P = 0.0003$), but was not associated with physical functioning or role physical.

The HRQL for the diabetic subjects with lower limb amputation found to be low compared to healthy diabetic reference subjects.

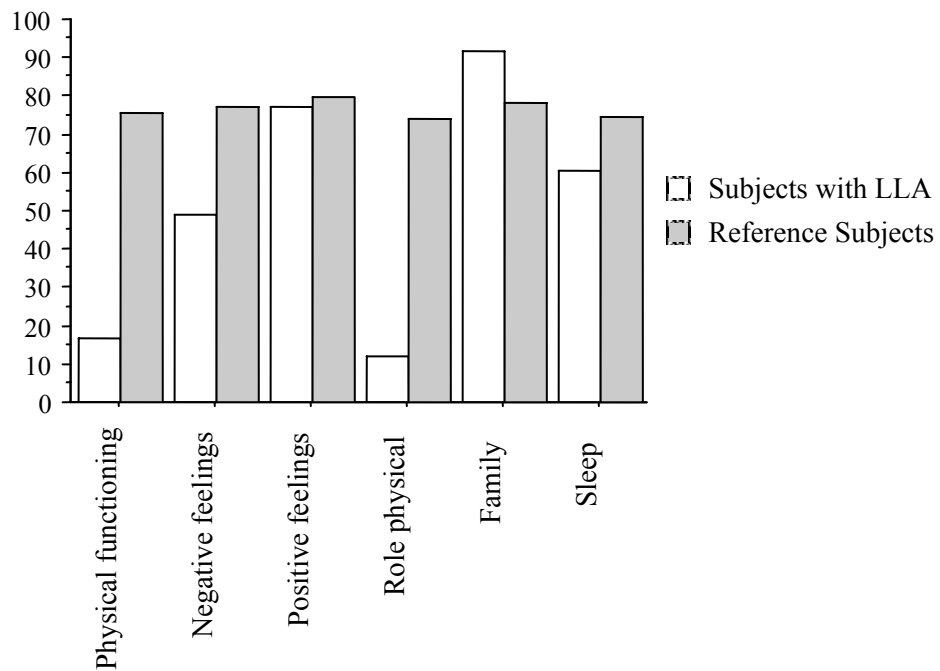


Figure 4. Mean values of the health-related quality of life (HRQL) scales in diabetic patients with LLA compared to reference subjects.

Conclusions

Paper (I)

In Sudanese subjects with type 2 diabetes, circulating leptin levels are lower in diabetic subjects than in controls of similar age and BMI. The lower serum leptin in diabetic subjects may be a consequence of differences in fat distribution or reduced insulin effect.

Paper (II)

The prevalence of maternal and neonatal complications among Sudanese diabetic women and their infants is high. The study confirms that also in this clinical setting, maternal hyperglycaemia emerges as an important factor affecting maternal well-being and neonatal morbidity and mortality.

Paper (III)

The comparison of glycaemic and insulin responses to six traditional Sudanese meals show differences of clinical importance, and could form a basis for dietary advice to diabetic subjects in Sudan and countries sharing similar food traditions to improve the glycaemic control and diabetes outcome.

Paper (IV)

Self-monitoring of both blood and urine glucose is not widely practiced among Sudanese diabetic patients, probably due to high cost and insufficient diabetes education. Self-monitoring in type 2 diabetic patients had little or no effect on glycaemic control, while, in contrast, self-monitoring was strongly linked to the glycaemic control in type 1 diabetic patients. Diabetes education and improving of health services at the primary level are important for the reduction of complications and burden of disease for the increasing group of Sudanese diabetes patients.

Paper (V)

Sudanese diabetic subjects with LLA had lower quality of life compared to healthy diabetic subjects. Multiple contributory factors influencing this lower quality of life, including duration of both disease and amputation, decreased sense of coherence and coping capacity and increased prevalence of general symptoms. However, functional and mobility status are suggested to play a potential role in determining the health related quality of life among this population. This puts serious emphasis on organization of health care for people with diabetes as a whole in Sudan, and on increasing the awareness by having intensive foot care programs.

General Conclusions and Future Perspectives

This thesis adds basic knowledge in two aspects, firstly, it puts serious emphasis on diabetes control and development of diabetes complications associated with pregnancy, and impact of the disease on quality of life and how local limited resources including simple traditional foods could be improved and utilized effectively targeting towards better diabetes care. Secondly, about diabetes mellitus and glucose metabolism, where findings lead to bigger circle of queries about whether type 2 diabetes among the Sudanese population has a different phenotype and the presence of the metabolic syndrome. Thus more studies are needed to fill the paucity of information in diabetes among Sudanese population.

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