



*Libyan International Medical University*  
Faculty of Pharmacy

# **Health Status of Diabetic Patients in the Eastern Region of Libya**

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## Declaration

This is to certify that research work embodied in this thesis entitled

**“Health Status Of Diabetic Patients In The Eastern Region Of Libya”**

has been carried out by us under supervision and guidance of Dr. Salma Bukhatwa.

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## **Abstract**

Diabetes mellitus (DM) is a chronic disorder of carbohydrate metabolism caused by abnormal insulin function or insulin deficiency, which results in elevated blood sugars. DM is a significant and growing health problem worldwide. Hence it is essential to understand the epidemiology for appropriate interventions. The main objective of this study was to examine the profile of diabetic patients in the Eastern region of Libya.

One hundred diabetic cases were randomly selected to participate in this study. Data collected by interviewing the patients and filling the questionnaire by the investigator depending on patient information and laboratory tests results.

Type 2 diabetes occurred in 92% of study sample while type 1 diabetes affected only 8% of study sample. Higher incidence of diabetes occurred in males (72%). Smokers represented 38% of study sample. Higher incidence of diabetes appeared among school attendant patients (45%) while the lowest incidence was among illiterate diabetics. Almost 63% of diabetic patients had a family history of diabetes. Current study showed that 80% of study sample were either overweight or obese. Most of diabetic patients suffered weakness (76%), muscle fatigue (38%), depression & sleeplessness (69%) or hypertension (50%). The most commonly used hypoglycemic drugs were biguanides, sulfonylureas and insulin. The adherence to diabetes therapy found was 83% of patients with (77%) of them used to have more than two drugs. Most of patients used to regularly monitor their blood glucose level. Among all clinical investigation tests results, only cholesterol, LDL, FBS, HbA1C all showed slightly higher values compared to reference values.

High percentage of risk factors including obesity, family history of diabetes, depression & hypertension requires a Libyan national policy for the surveillance, prevention and control of diabetes and its complications.

## Table of Contents

<b>ABSTRACT</b>	<b>3</b>
<b>LIST OF TABLES</b>	<b>6</b>
<b>LIST OF FIGURES</b>	<b>6</b>
<b>LIST OF ABBREVIATIONS</b>	<b>7</b>
<b>ACKNOWLEDGEMENT</b>	<b>8</b>
<b>GENERAL INTRODUCTION</b>	<b>10</b>
<b>BACKGROUND</b>	<b>10</b>
<b>EPIDEMIOLOGY</b>	<b>11</b>
<b>TYPES OF DIABETES</b>	<b>12</b>
<b>TYPE 1 DIABETES</b>	<b>12</b>
<b>TYPE 2 DIABETES</b>	<b>12</b>
<b>GESTATIONAL DIABETES</b>	<b>12</b>
<b>SPECIFIC TYPES OF DIABETES</b>	<b>12</b>
<b>DIAGNOSIS OF DIABETES MELLITUS</b>	<b>13</b>
<b>RANDOM BLOOD GLUCOSE</b>	<b>13</b>
<b>FASTING BLOOD GLUCOSE</b>	<b>13</b>
<b>ORAL GLUCOSE TOLERANCE TEST</b>	<b>13</b>
<b>IMPAIRED GLUCOSE TOLERANCE AND IMPAIRED FASTING GLYCAEMIA</b>	<b>14</b>
<b>GLYCATED HAEMOGLOBIN</b>	<b>14</b>
<b>RISK FACTORS FOR DIABETES MELLITUS</b>	<b>14</b>
<b>RISK FACTORS FOR TYPE 1 DIABETES</b>	<b>15</b>
<b>RISK FACTORS OF TYPE 2 DIABETES</b>	<b>15</b>
<b>ETIOLOGY OF DIABETES MELLITUS</b>	<b>16</b>
<b>ETIOLOGY OF TYPE 1 DIABETES</b>	<b>16</b>
<b>GENETIC SUSCEPTIBILITY</b>	<b>16</b>
<b>AUTOIMMUNE DESTRUCTION OF B-CELLS</b>	<b>17</b>
<b>ENVIRONMENTAL FACTORS</b>	<b>17</b>
<b>ETIOLOGY OF TYPE 2 DIABETES</b>	<b>17</b>
<b>GENETIC SUSCEPTIBILITY</b>	<b>17</b>
<b>OBESITY AND PHYSICAL INACTIVITY</b>	<b>18</b>
<b>B-CELL DYSFUNCTION</b>	<b>18</b>
<b>ABNORMAL GLUCOSE PRODUCTION BY LIVER</b>	<b>18</b>
<b>ETIOLOGY OF GESTATION DIABETIC</b>	<b>20</b>
<b>ETIOLOGY OF OTHER TYPES OF DIABETES</b>	<b>20</b>
<b>MANAGEMENT THERAPY OF DIABETES</b>	<b>20</b>
<b>DIET</b>	<b>21</b>
<b>EXERCISE</b>	<b>21</b>

<b>INSULIN THERAPY</b>	<b>21</b>
CLASSIFICATION OF INSULIN	21
INHALED INSULIN	21
<b>ORAL ANTIDIABETIC MEDICINES</b>	<b>22</b>
SULFONYLUREAS	22
BIGUANIDES	22
ALPHA-GLUCOSIDASE INHIBITORS	22
THIAZOLIDINEDIONES	22
MEGLITINIDES	23
<b><u>OBJECTIVES OF THE WORK</u></b>	<b><u>23</u></b>
<b><u>DATA COLLECTION</u></b>	<b><u>25</u></b>
<b><u>DATA COLLECTION TOOL</u></b>	<b><u>25</u></b>
<b><u>DATA ANALYSIS</u></b>	<b><u>26</u></b>
<b>1. BASELINE CHARACTERISTICS OF STUDY SUBJECTS</b>	<b>29</b>
<b>2. FAMILY HISTORY OF DIABETES AMONG STUDY SUBJECTS</b>	<b>31</b>
<b>3. RISK FACTORS &amp; COMMON SYMPTOMS</b>	<b>32</b>
<b>4. DRUG (S) CONSUMPTION</b>	<b>33</b>
<b>5. REGULAR MONITORING OF BLOOD GLUCOSE LEVEL</b>	<b>34</b>
<b>6. CLINICAL INVESTIGATION TESTS</b>	<b>35</b>
<b>DISCUSSION</b>	<b>37</b>
<b>CONCLUSION</b>	<b>40</b>
<b>REFERENCE</b>	<b>42</b>

## List of Tables

TABLE 1: CLINICAL CHARACTERISTICS OF PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS .....	13
TABLE 2: DIAGNOSTIC CRITERIA FOR DIABETES AND INTERMEDIATE HYPERGLYCEMIA .....	14
TABLE 3: DIFFERENT TYPES OF INSULIN .....	22
TABLE 4: BASELINE CHARACTERISTICS OF STUDY SUBJECTS .....	30
TABLE 5: CLINICAL INVESTIGATION TESTS .....	35

## List of Figures

FIGURE 1: GLUCONEOGENESIS AND GLYCOGENOLYSIS .....	19
FIGURE 2: KETONES PRODUCTION BY LIVER DURING FASTING CONDITION .....	19
FIGURE 3A: QUESTIONNAIRE USED IN THE STUDY (PAGE 1) .....	27
FIGURE 3B: QUESTIONNAIRE USED IN THE STUDY (PAGE 1) .....	27
FIGURE 4: DIABETIC PATIENTS AND FAMILY HISTORY OF THE DISEASE .....	31
FIGURE 5: DIABETIC PATIENTS AND DETAILED FAMILY HISTORY OF THE DISEASE .....	31
FIGURE 6: RISK FACTORS AND COMMON SYMPTOMS AMONG STUDY SUBJECTS .....	32
FIGURE 7: ADHERENCE OF DIABETIC PATIENTS TO TREATMENTS .....	33
FIGURE 8: NUMBER OF DRUGS CONSUMED BY DIABETIC PATIENTS .....	33
FIGURE 9: THE MOST COMMONLY USED DRUGS BY DIABETIC PATIENTS .....	34
FIGURE 10: REGULAR MONITORING OF BLOOD GLUCOSE LEVEL .....	34

## List of Abbreviations

ACEIs	Angiotensin Converting Enzyme Inhibitors
ARABs	Angiotensin II Receptor Blockers
BMI	Body Mass Index
CBC	Complete Blood Count
CMV	Cytomegalovirus
CV	Cardiovascular
DIDMOAD	Diabetes Insipidus, Diabetes Mellitus Optic Atrophy and Deafness
DM	Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
Hb	Hemoglobin
HDL	High Density Lipoprotein
IDF	International Diabetes Federation
IFG	Impaired Fasting Glycaemia
IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Disease
K <sup>+</sup>	Potassium
LDL	Low Density Lipoprotein
MODY	Maturity Onset Diabetes of The Young
Na <sup>+</sup>	Sodium
NIDDM	Non Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
SD	Standard Deviation
SEM	Standard error of the mean
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

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# Chapter I

## Introduction

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## General Introduction

Diabetes mellitus (DM) is real medical problem that affects the world as a whole and Libya in particular. Generally the world health organization (WHO) has projected that over the period of next 25 years globally the number of patients suffering from DM will be doubled or more and devolving countries will bear most of the sufferers.<sup>1</sup> The rate of diabetic patients with major complications are increased such as stroke, hypertension, amputation, nephropathy, neuropathy, retinopathy, cardiovascular, impotence, and skin lesion.<sup>2</sup> However, in the eastern Mediterranean, the essential health care and facilities for self-care are often inadequate, also the deficient in basic education services and knowledge on diabetes as well as its prevention, management and treatment to people with diabetes and their families which lead to serious impediment to the provision of minimum standard of health care.<sup>3</sup> The causes of DM is multifactorial, which include genetic, physical inactivity, drug toxic agents, obesity, viral infection and location.<sup>4</sup>

Although, the health services in Libya are free of charge and patients are provided with oral hypoglycemic drugs, human insulin and syringes free of charge. In this country the diabetes considered as the fourth leading cause of death in 2012, according to the WHO.<sup>5</sup> DM classified in to three major types as type 1, type 2, and gestational diabetes in addition to a rare types due to specific causes.<sup>6</sup> Controlling of hyperglycemia can be difficult and can require, in addition to lifestyle changes, oral antidiabetics and sometimes insulin.<sup>7</sup>

## Background

DM is more common endocrine disorder engaged with clinical practice. It may be defined as a syndrome characterized by increase the glucose blood level (hyperglycaemia) due to an insulin resistance and an absolute or relative lack of insulin.<sup>8</sup> Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. As result of lacking of insulin, the cells are unable to take up glucose. Regardless of the reason, the glucose level continue to increasing more than ability of kidneys to filtrate it, which led to exceeded glucose in blood spills into the urine.<sup>9,10</sup>

If insulin secretion is increased, blood glucose levels may become very low (hypoglycemia) as large amounts of glucose enter tissue cells and little remains in the bloodstream. Multiple hormones may affect glycaemia. Insulin is the only hormone that lowers blood glucose levels. The counter-regulatory hormones such as glucagon, catecholamines, growth hormone, thyroid hormone, and glucocorticoids all act to increase blood glucose levels, in addition to their other effects.<sup>11</sup> The more common signs and symptoms of hyperglycemia include polyuria, nocturia, chronic fatigue, malaise, polydipsia, polyphagia, vision abnormalities, weight loss and recurrent infection.<sup>12</sup>

## Epidemiology

According to the WHO global report of 2003, there are approximately 171 million diabetic patients around the world and this number of diabetic patients increases to reach 366 million patients worldwide by the year 2030.<sup>13,14</sup>

In 2007 the International Diabetes Federation IDF estimated that diabetes affects 246 million people worldwide and is predicted to affect 380 million patients by 2025, also estimated that 7.3% of adult aged 20-79 in all IDF member countries have diabetes.<sup>15</sup> The major these increases will happen in developing countries in Asia and Africa.<sup>16</sup>

Prevalence of known diabetes in Britain is around 2-3%, while in the Middle East and Far East is high about 12% in the Indian subcontinent. The prevalence of type 2 diabetes increases occur in migrant population to industrialized countries, as in Asian and Afro-Caribbean immigrations to the United kingdom. Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide.<sup>17</sup> Type 1 diabetes is common in Caucasian population and in northern Europe. In Europe and North America the ratio of type 2 to type 1 is approximately 7:3. Diabetes is a major burden upon health-care facilities in all countries.<sup>12</sup> Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus.<sup>18</sup> The prevalence of type 2 ranged from 4.6 to 40% in the middle east, 0.3 to 17.9% in Africa, 1.2 to 14.6% in Asia, 0.7 to 11.6% in Europe, 6.69 to 28.2% In north of America.<sup>19-21</sup>

Study by El Mugamer and his colleagues (1995) found that diabetes prevalence was 6% (11% in male and 7% in female aged 30-64 years).<sup>22</sup>

A cross sectional study by Jamil and his colleagues (2008) estimated the prevalence of diabetes among whites (n=212), Arabs (n=1303), Chaldeans (n=628), and black (n=789), in south east Michigan, the overall prevalence of diabetes was 7.0% and the highest was for black 8.0% followed by Arabs and white 7.0% for each group and 6.0% for Chaldeans (p 0.005).<sup>23</sup> Study in Benghazi by Kadiki and Roaeid (2001) showed that prevalence of DM was

14.1%.<sup>24</sup> WHO report about Libya (2013) revealed that raised blood glucose in adult aged 25+ of male and female was 14.5 % and 14.4% respectively.<sup>5</sup>

## **Types of diabetes**

Diabetes can be classified into three common types type 1, type 2, gestational diabetes in addition to other specific types.

### **Type 1 diabetes**

Type 1 diabetes was previously termed insulin dependent diabetes mellitus (IDDM), which is usually first diagnosed in children, teenagers, and young adults. Type 1 indicates the process of beta-cell destruction in the pancreas that may ultimately lead to diabetes mellitus in which “insulin is required for survival” to prevent the development of ketoacidosis, coma and death because the body’s immune system has attacked and destroyed them.<sup>25</sup> The clinical characteristics of patients with type 1 and type 2 diabetes mellitus are shown in Table 1.

### **Type 2 diabetes**

Type 2 diabetes was previously termed non-insulin-dependent diabetes mellitus (NIDDM) because patients retain the capacity to secrete some insulin but exhibit impaired sensitivity to insulin (insulin resistance) and can usually be treated without insulin replacement therapy. About 20% of type 2 diabetic patients develop to insulin deficiency requiring replacement therapy.<sup>12</sup>

### **Gestational diabetes**

During normal pregnancy, insulin sensitivity is reduced through action of placental hormones and this affects glucose tolerance. The term gestational diabetes refers to hyperglycemia occurring for the first time during pregnancy.<sup>12</sup> Gestational diabetes usually goes away after the baby is born. Shortly after pregnancy, 5-10% of women with gestational diabetes continue to have high blood glucose levels and are diagnosed as having diabetes, usually type 2.<sup>26</sup>

### **Specific types of diabetes**

Other types of diabetes include those caused by genetic defects, diseases of the pancreas, excess amounts of certain hormones resulting from some medical conditions, medications that reduce insulin action, chemicals that destroy beta cells, infections, rare autoimmune disorders, and genetic syndromes associated with diabetes.<sup>26</sup>

**Table 1: Clinical characteristics of patients with type 1 and type 2 diabetes mellitus**

Features	Type 1	Type 2
Age of onset	Usually less than 20 years	Usually greater than 30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Thiazolidinediones, metformin, sulfonylureas or insulin

*Adapted from Guyton and Hall<sup>27</sup>*

## **Diagnosis of diabetes mellitus**

The formal diagnosis of diabetes mellitus requires analysis of at least one blood sample. A fasting sample is preferred and random sample may be acceptable. If the diagnosis is not clear from fasting and/or random sample, the oral glucose tolerance test may be required.<sup>8</sup>

### **Random blood glucose**

If a patient complains of hyperglycaemia symptoms, a random blood glucose result of  $\geq 11.1$  mmol/L (200mg/dl) may be used to diagnose diabetes. If the patient is asymptomatic or there is any doubt about the diagnosis, a repeat sample is required but preferable fasting.<sup>8</sup>

### **Fasting blood glucose**

A fasting blood glucose concentration of  $\geq 7.0$  mmol/L (126mg/dl) is regarded as diagnosis of diabetes whether or not hyperglycemic symptoms are present. The patient should be fasted at least 10 hours. If the result falls between 6.1 (110mg/dl) and 6.9 mmol/L (125mg/dl), the patient is said to have 'impaired fasting glycaemia'.<sup>8</sup>

### **Oral glucose tolerance test**

Sometimes diagnostic confusion still exists even after a repeat sample has been analyzed, e.g. borderline or apparently conflicting results. In this situation an oral glucose tolerance test (OGTT) is recommended. A normal diet should have been consumed for at least 3 days prior to the test. A fasting sample is collected immediately before an oral glucose load (75g of glucose in about 300ml of water); this should be drunk within 5 minutes or so. A second sample is collected 2 hours later. The patient should be relatively inactive throughout and smoking is prohibited throughout the test.<sup>8</sup>

## Impaired glucose tolerance and impaired fasting glycaemia

Impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) are intermediate categories of glycaemia that fall short of the diagnosis of diabetes, but which define an increased risk of developing diabetes. IGT can only be diagnosed after an oral glucose tolerance test. The risks associated with IGT (e.g. risk of developing diabetes) are well-defined and can be characterized over many years. By contrast, IFG is diagnosed from a single fasting sample. Its existence as a diagnosed category arose out of the 1997 recommendation of the American Diabetes Association that oral glucose tolerance tests be abandoned in favour exclusively of fasting samples (this recommendation was not adopted by the WHO when it updated its 1985 diagnostic criteria in 1999). The criteria for IFG are arbitrary and the associated risks less well-defined than for IGT.<sup>8</sup>

## Glycated haemoglobin

Currently HbA1c is not considered a suitable diagnostic test for diabetes or intermediate hyperglycaemia.<sup>14</sup> The WHO criteria for diagnosing of DM are shown in table (2).

**Table 2: Diagnostic criteria for diabetes and intermediate hyperglycemia**

Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl) or
2-h plasma glucose*	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl) ≥7.8 and <11.1mmol/l
2-h plasma glucose*	(and 140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)
2-h plasma glucose*	and (if measured) <7.8mmol/l (140mg/dl)

\* Venous plasma glucose 2-h after ingestion of 75g oral glucose load

\* If 2-h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

*Adapted from WHO and IDF (2006)<sup>14</sup>*

## Risk factors for diabetes mellitus

Obesity and inactive lifestyle are risk factors associated with diabetes, these risk factors can be controlled, in contrast to ethnicity, age, sex and genetics which are uncontrollable risk factors.<sup>28</sup>

## **Risk factors for type 1 diabetes**

The primary risk factor for type 1 diabetes is a family history of this lifelong, chronic disease. Having family members with diabetes is a major risk factor.<sup>28</sup> Regarding to age and gender the risk of IDDM increases with age during childhood and adolescence. However, there is a decline in incidence of IDDM during adulthood.<sup>29</sup> Green et al 1992, have provided clear evidence that racial and ethnic background represents one of the most important risk factors for IDDM.<sup>30</sup> Some study showed that More than 80% of cases of IDDM occur in individuals with no family history of the disease. The overall risk before age 30 years for North American Caucasian siblings, parents, and offspring of individuals with IDDM ranges from 1% to 15%.<sup>31</sup> For environmental factors in the etiology of IDDM. Nutrition and viruses have been suggested as potential determinants of the disease. However, a positive association between ingestion of smoked/cured mutton by Icelandic women at conception and subsequent development of IDDM in their offspring was reported.<sup>32</sup> Viral infections as possible triggers of autoimmune disease. The incorporation of human cytomegalovirus (CMV) gene segments into genomic DNA has been significantly associated with IDDM in newly diagnosed patients, and a relationship between CMV genome positivity and islet cell antibodies has also been reported.<sup>33</sup> Persistent CMV infection may lead to the expression of viral or host antigens on the  $\beta$ -cells of the pancreas,<sup>34</sup> Other potential risk factors In addition to nutrition and viruses, other potential IDDM risk factors include stress, maternal age, birth order, and socioeconomic status. Several investigators noted that life events such as accidents, pregnancy, and personal problems frequently occurred during the year prior to IDDM onset.<sup>35</sup> These observations were supported by a family study that revealed an increase in the reporting of at least one serious life event during the 6 months prior to disease onset in IDDM compared with no diabetic siblings.<sup>36</sup> Although investigations of stress and IDDM have, in general, reported positive associations, most studies have been retrospective and suffered from methodological difficulties in assessing stress and measuring its frequency, intensity, and duration.<sup>37,38</sup> Thus, prospective evaluations of the interaction among stress, the immune system, and the occurrence of autoimmune diseases are warranted. Earlier reports indicating that either high or low socioeconomic status was related to IDDM incidence are conflicting.<sup>39</sup>

## **Risk factors of type 2 diabetes**

The risk factors associated with type 2 diabetes include obesity, diet and physical inactivity, increasing age, insulin resistance, and family history of diabetes, genetic factors, race and ethnicity. As concerns genetic factors, research has shown that certain gene variations raise

the risk of developing diabetes.<sup>40</sup> People aged 40 to 60 years (that is, working age) are affected most, compared with those older than 60 years in developed countries.<sup>41</sup> In most populations, NIDDM incidence is low before age 30 years but increases rapidly with older age. The prevalence of diabetes in Pima Indians aged 25-29 years (13%) is, however, as high as that for U.S. non-Hispanic whites age 60-64 years.<sup>42</sup> Weight in developing countries and the rise in prevalence of overweight and obesity are important risk factors.<sup>43</sup> Regarding to ethnicity of NIDDM is approximately twice as common in blacks and Hispanics as in non-Hispanic whites.<sup>44</sup> Diet has been considered a possible cause of diabetes for centuries.<sup>45</sup> In a small sample of Pima Indian women, higher total and complex carbohydrate intake were associated with higher NIDDM incidence, but comparisons were not adjusted for higher total calorie intake, weight gain, obesity, and other factors physical activity.<sup>46</sup> Ecologic studies, suggest that NIDDM prevalence is consistently lower in populations with higher levels of habitual physical activity.<sup>47,48</sup> Numerous studies show that obesity is associated with NIDDM prevalence.<sup>45</sup> Other studies have shown that, as persons age, both weight gain and increased waist circumference occur; even in older persons who lose weight, waist circumference continues to increase. Such trends may partially account for the increased incidence of NIDDM with aging.<sup>49</sup> Regarding to socioeconomic status more studies have found that lower income, education, and social class are associated with increased prevalence of NIDDM.<sup>50</sup> The NIDDM, atherosclerosis, and hypertension share several critical risk factors, including dietary fat, physical inactivity, and upper body obesity. Increased triglycerides and decreased HDL levels have been consistently associated with NIDDM.<sup>51</sup> vLDL concentration was an independent predictor of glucose intolerance in a 14 year follow-up of the Framingham Study in Massachusetts.<sup>52</sup> A 10-year follow up of subjects with familial hypertriglyceridemia demonstrated that the baseline NIDDM and IGT incidence, independent of insulin levels.<sup>53</sup> A significantly decreases in plasma HDL-cholesterol were observed in type 2 diabetes patients with IHD than type 2 patient without IHD.<sup>54</sup>

## **Etiology of Diabetes mellitus**

### **Etiology of type 1 diabetes**

#### **Genetic susceptibility**

Heredity plays an important part in determining who is likely to develop type 1 diabetes. Many genes, as well as interactions among genes, are thought to influence susceptibility to and protection from type 1 diabetes. While HLA genes are the major risk genes for type 1 diabetes, many additional risk genes or gene regions have been found. Not only can these



genes help identify people at risk for type 1 diabetes, but they also provide important clues to help scientists better understand how the disease develops and identify potential targets for therapy and prevention.<sup>55</sup>

### **Autoimmune destruction of $\beta$ -cells**

In type 1 diabetes, white blood cells called T cells attack and destroy  $\beta$ -cells. The process begins well before diabetes symptoms appear and continues after diagnosis. Often, type 1 diabetes is not diagnosed until most beta cells have already been destroyed. At this point, a person needs daily insulin treatment to survive.<sup>55</sup>

### **Environmental factors**

Environmental factors, such as foods, viruses, and toxins, may play a role in the development of type 1 diabetes, but the exact nature of their role has not been determined. Some theories suggest that environmental factors trigger the autoimmune destruction of beta cells in people with a genetic susceptibility to diabetes. Other theories suggest that environmental factors play an ongoing role in diabetes, even after diagnosis.<sup>55</sup> A virus cannot cause diabetes on its own, but people are sometimes diagnosed with type 1 diabetes during or after a viral infection, suggesting a link between the two. Also, the onset of type 1 diabetes occurs more frequently during the winter when viral infections are more common. Viruses possibly associated with type 1 diabetes include coxsackievirus B, CMV, adenovirus, rubella, and mumps. Scientists have described several ways these viruses may damage or destroy beta cells or possibly trigger an autoimmune response in susceptible people. For example, anti-islet antibodies have been found in patients with congenital rubella syndrome. Scientists are trying to identify a virus that can cause type 1 diabetes so that a vaccine might be developed to prevent the disease.<sup>55</sup>

## **Etiology of Type 2 diabetes**

### **Genetic Susceptibility**

The role of genes is suggested by the high rate of type 2 diabetes in families and identical twins and wide variations in diabetes prevalence by ethnicity. Type 2 diabetes occurs more frequently in African Americans, Alaska Natives, American Indians, Hispanics/Latinos, and some Asian Americans, Native Hawaiians, and Pacific Islander Americans than it does in non-Hispanic whites. Recent studies have combined genetic data from large numbers of people, accelerating the pace of gene discovery. Genes can also increase the risk of diabetes by increasing a person's tendency to become overweight or obese.<sup>55</sup>

The concordance of type 2 diabetes in monozygotic twins (~70%) is much higher compared to dizygotic twins (20–30%). A family history confers first-degree relatives a 3-fold increase in risk of developing type 2 diabetes. It has also been suggested that ethnic differences in the prevalence of type 2 diabetes could be ascribed to genetic differences. Classic genetic research conducted with twins and with biological and adoptive families, consistently supports genetic links to type 2 diabetes. However, until very recently, type 2 diabetes susceptibility genes have been poorly understood. With the recent advent of genome-wide association studies, a number of type 2 diabetes susceptibility loci have been.<sup>56</sup>

### **Obesity and physical inactivity**

Obesity and physical inactivity are strongly associated with the development of type 2 diabetes. People who are genetically susceptible to type 2 diabetes are more vulnerable when these risk factors are present. An imbalance between caloric intake and physical activity can lead to obesity, which causes insulin resistance and is common in people with type 2 diabetes. Central obesity, in which a person has excess abdominal fat, is a major risk factor not only for insulin resistance and type 2 diabetes but also for heart and cardiovascular diseases (CV). This excess “belly fat” produces hormones and other substances that can cause harmful, chronic effects in the body such as damage to blood vessels.<sup>55</sup>

### **β-cell dysfunction**

Type 2 diabetes is characterized by a progressive loss of β-cell function throughout the course of the disease. The pattern of loss is an initial defect in early or first-phase insulin secretion, followed by a decreasing maximal capacity of glucose to potentiate all nonglucose signals. Last, a defective steady-state and basal insulin secretion develops, leading to complete β-cell failure requiring insulin treatment.<sup>57</sup>

### **Abnormal glucose production by liver**

The liver supplies sugar or glucose by turning glycogen into glucose in a process called glycogenolysis (Figure 1). The liver also can manufacture necessary sugar or glucose by harvesting amino acids, waste products and fat byproducts. This process is called gluconeogenesis (Figure 1).

When body's glycogen storage is running low, the body starts to conserve the sugar supplies for the organs that always require sugar. These include: the brain, red blood cells and parts of the kidney. To supplement the limited sugar supply, the liver makes ketones from fats. This process is called ketogenesis (Figure 2). The hormone signal for ketogenesis to begin is a low level of insulin. Ketones are burned as fuel by muscle and other body organs. And the sugar is saved for the organs that need it.<sup>58</sup>

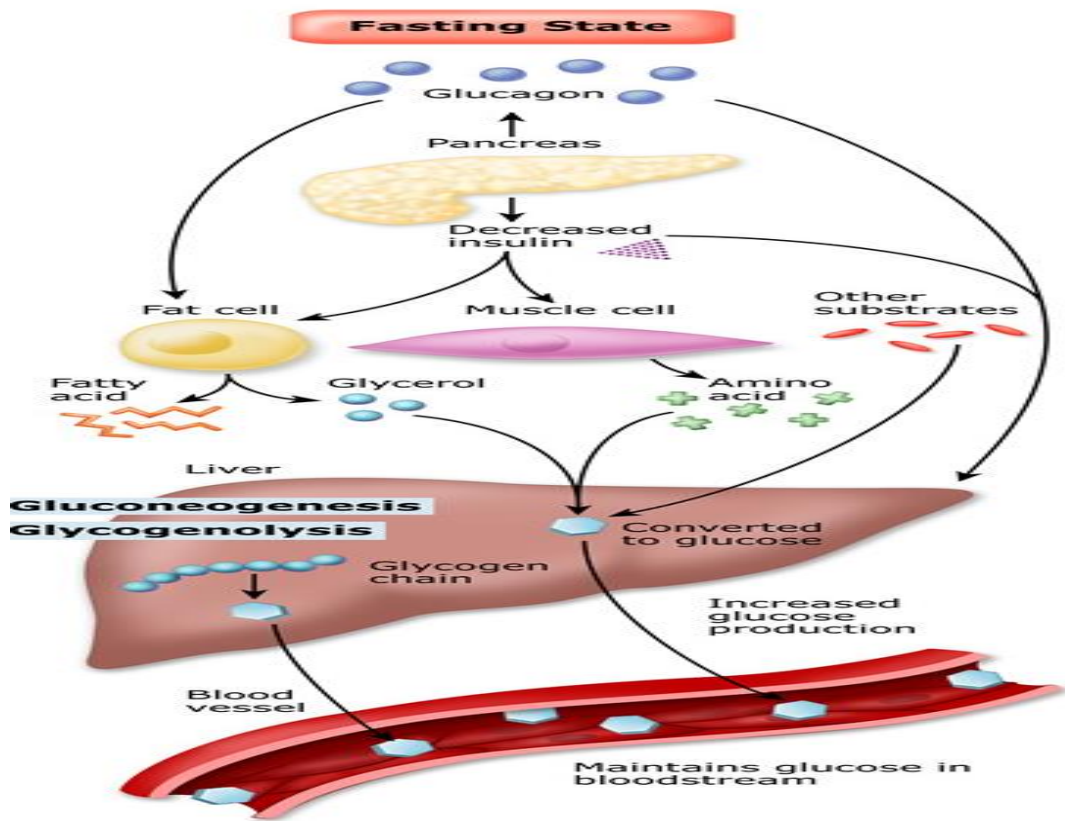


Figure 1: Gluconeogenesis and glycogenolysis

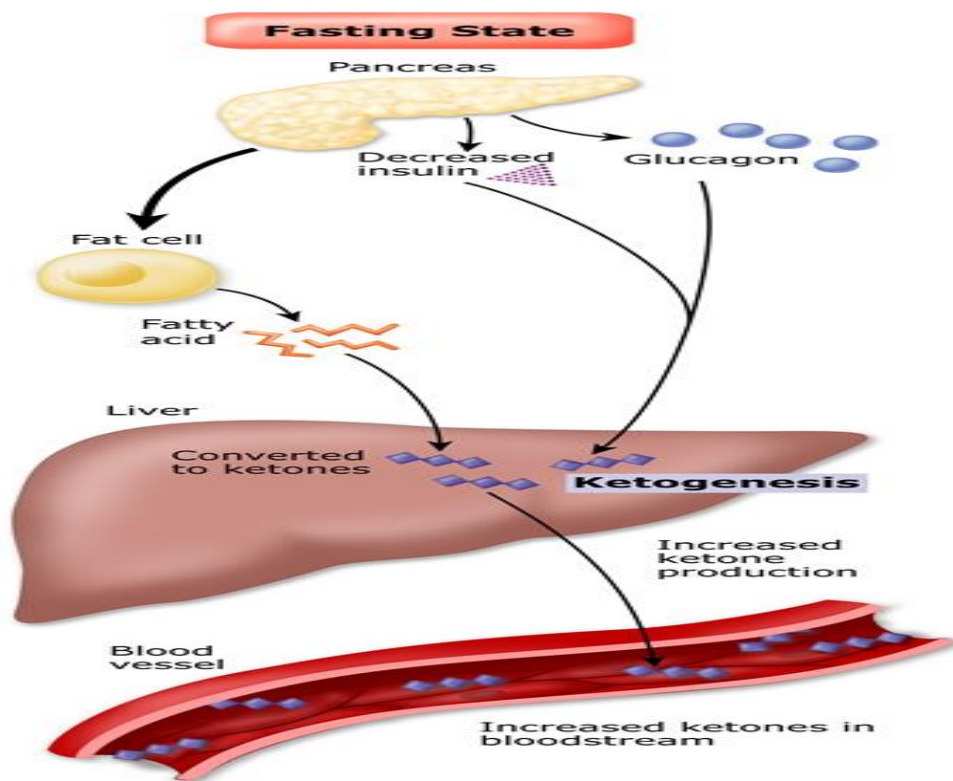


Figure 2: Ketones production by liver during fasting condition

## **Etiology of gestational diabetes**

Any woman might develop gestational diabetes during pregnancy. Some of the factors associated with women who have an increased risk are obesity; a family history of diabetes; have given birth previously to a very large infant, a stillbirth, or a child with a birth defect; or having too much amniotic fluid (polyhydramnios). Also, women who are older than 25 are at greater risk than younger individuals. Although a history of sugar in the urine is often included in the list of risk factors, this is not a reliable indicator of who will develop diabetes during pregnancy. Some pregnant women with perfectly normal blood sugar levels will occasionally have sugar detected in their urine.<sup>59- 60</sup>

## **Etiology of other types of diabetes**

Maturity onset diabetes of the young (MODY) is a rare form of diabetes, which is different from both type 1 and type 2 diabetes, and runs strongly in families. MODY is caused by a mutation in a single gene. If a parent has this gene mutation, any child they have, has a 50 per cent chance of inheriting it from them. If a child does inherit the mutation they will generally go on to develop MODY before they are 25, whatever their weight, lifestyle, or ethnic group.

Neonatal diabetes is a form of diabetes that is diagnosed under the age of six months. It is a different type of diabetes than the more common type 1 diabetes as it is not an autoimmune condition.

Wolfram syndrome is the association of diabetes mellitus and optic atrophy, and is sometimes called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Incomplete characterization of this autosomal recessive syndrome has relied on case-reports, and there is confusion with mitochondrial genome disorders. We therefore undertook a UK nationwide cross-sectional case-finding study to describe the natural history, complications, prevalence, and inheritance of the syndrome.

Alström Syndrome is a rare genetically inherited syndrome, which has a number of common features.<sup>61</sup>

## **Management therapy of diabetes**

There is no cure for type 1 diabetes. Treating either type 1 diabetes or type 2 diabetes involves medicines, diet, and exercise to control blood sugar level. Healthcare provider should be an educator to diabetic patients about their disease risk factors, and management complications.

## **Diet**

The ideal diabetic diet should consist of 50-60 % complex carbohydrates, 15-20 % proteins, and the remainder fat. Simple sugars should be avoided .<sup>62</sup>

## **Exercise**

Regular exercise has been shown to improve blood glucose control, reduce CV risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent Type 2 diabetes in high-risk individuals.<sup>(63-65)</sup>

### **Treatment of diabetes**

Type 2 diabetes may be reversed with lifestyle changes, especially losing weight with Exercise and by eating healthier foods. Some cases of Type 2 diabetes can also be improved with weight-loss surgery.

## **Insulin therapy**

### **Classification of insulin**

Rapid acting insulin. Insulin lispro, insulin aspart and insulin glulisine

Short acting - insulin Regular (R) is also known as soluble insulin. Insulin regular used to be manufactured from beef and pork pancreas but is now available as human recombinant insulin. All brands of insulin from beef or pork origin have now been discontinued (table3).

Intermediate acting - insulin isophane (N), insulin zinc (also known as lente (L)

### **Inhaled Insulin**

Exubera is a rapid-acting form of human insulin that is inhaled through the mouth. It works by lowering levels of glucose in the blood. Exubera was withdrawn from the U.S. market in 2007 due to lack of consumer demand for the product. No drug safety concerns were cited in this withdrawal.

Premixed insulin has two types of insulin mixed together in one vial. These are called biphasic insulin. This makes it easier to inject two different types of insulin at the same time. Profile of the premixed insulin depends on the combination. Normally, one insulin will be rapid or short acting and the other one have a longer duration of action.<sup>(66)</sup>

**Table 3: Different types of insulin**

<b>Generic Name</b>	<b>Onset</b>	<b>Peak</b>	<b>Duration</b>
Insulin glulisine	10 to 20 mins	55 mins	3 hours
Insulin lispro	15 mins	1 to 1.5 hours	2 to 5 hours
Insulin aspart	10 to 20 mins	1 to 3 hours	3 to 5 hours
Insulin regular	30-60 mins	2 - 5 hours	6 - 8 hours
Insulin isophane	1 to 1.5 hours	6 to 12 hours	15 to 24 hours

### **Oral antidiabetic medicines**

Oral medications are used in the treatment of type 2 diabetes.

#### **Sulfonylureas**

Sulfonylureas work by stimulating the pancreas to release more insulin and are only effective when there is some pancreatic beta-cell activity still present. Non-obese patients with Type 2 diabetes are usually started on sulfonylureas. A common side effect is hypoglycemia. It may cause weight gain .<sup>66</sup>.

#### **Biguanides**

Metformin is the only available biguanide. It inhibits the amount of glucose produced by the liver, increases the insulin-receptor binding and stimulates tissue uptake of glucose. Metformin does not stimulate the pancreas to make or release more insulin. It does not cause hypoglycaemia or weight gain therefore obese patients with type 2 diabetes are usually started on biguanides. Common side effects include abdominal discomfort, diarrhea, nausea or vomiting, loss of appetite, and metallic taste.<sup>66</sup>

#### **Alpha-glucosidase inhibitors**

Alpha-glucosidase inhibitors slow the digestion of carbohydrates and delay glucose absorption. They work by inhibiting intestinal enzymes that digest carbohydrates, thereby reducing carbohydrate digestion after a meal, which lowers postprandial blood glucose elevation in diabetics.<sup>66</sup>

#### **Thiazolidinediones**

Thiazolidinediones (also called glitazones) work by making the body's cells more sensitive to insulin, so less insulin is needed to move glucose from the blood into the cells. This leads to a reduction of blood glucose levels.<sup>66</sup>

### **Meglitinides**

Meglitinides works by stimulating the pancreas to release insulin in response to a meal. Hypoglycemia is a common side effect. <sup>(66-67)</sup>

### **Objectives of the work**

The main objective of this study was to examine the profile of diabetic patients in the Eastern region of Libya.

# Chapter II

## Materials and Methods

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## Data collection

Data were collected from 12-7-2015 to 18- 8-2015 from clinics in Benghazi and Albeida cities. One hundred patients aged from 20-70 years old were participated in this study. Data collected by inter review the patient and filling the questionnaire by the investigator depended on patient information and laboratory tests.

## Data collection tool

A structured questionnaire was used (Figures 3a & 3b).

First part of the questionnaire included general data of patient, as follow:

Age, sex, ethnicity, weight, height, waist, size, body mass index (BMI), monthly income, education and smoking (Figure 3a).

Second part of the questionnaire included information about the disease as follow:

Duration of diabetes, type of diabetes, family history, risk factors such as HTN, IHD, kidney disease and diabetic coma. Any other symptoms like muscle fatigue, nausea, weakness, itching, depression, stress or sleeplessness (Figure 3a).

Third part of the questionnaire other factors affected the disease were reported as follow:

Daily physical activity: how many times per week and for how much time.

3. Daily intake of fruits and vegetables and special diet.
4. Daily water intake liters.
5. Patient adherence to treatment.

Fourth part of the questionnaire included drug treatment received by patient, and adherence of patient to regular monitoring of blood glucose level were reported (Figure 3b) .

Last part of the questionnaire included the clinical investigation tests done by patients and reported, as follow:

Fasting blood glucose, HbA<sub>1</sub>C , cholesterol , triglycerides , HDL , LDL , VLDL, urea and Creatinine, Na<sup>+</sup> and K<sup>+</sup>, CBC concentrating on WBC, neutrophils, lymphocytes and HB (Figure 3b).

## Data analysis

All data was presented as Mean  $\pm$  SEM (n) or percentage (%) when needed. Excel was used for statistical analysis of results.

**QUESTIONNAIRE**

No.  Date.  /  /2015

Age  Gender male  female  Ethnicity. black  white

Weight  Height  Waist size

Body mass index (BMI) <18.5  18.5 – 24.9  25 – 29.9  30 – 39.9

Income monthly. <500 LD  500 LD  1000 LD  1500 LD >  1500 LD

Education- Illiterate  Primary school.  High education

Smoking yes  No

Duration of diabetes. 1 - 5  5 - 10  more 10 years

Type of diabetes. Type I  Type II

Anyone from family suffering from diabetes yes  No

Type I  Type II  relation

Coexistent risk factors. hypertension  ischemic heart disease  Kidney disease   
diabetic coma

symptoms as muscle fatigue  nausea  weakness  itching

Suffering from depression, stress, sleeplessness Yes.  No.

Daily/Physical activity Yes.  No.  Days/week  $3 \leq$    $3 \geq$   time/ m 30  60  60 >

Daily intake of fruits & vegetables Yes  No  Special diet Yes  No

Daily water intake  $\leq 1L$   2L   $\geq 2.5L$

Adherence with treatment. Yes.  No

(1)

Figure 3a: Questionnaire used in the study (page 1)

**Treatment taking.**

Antidiabetic agent		Antihypertensive		Antihyperlipidemic		others
sulphonylureas		ACEIs & ARBs		Alternative medicine		
biguanides		Ca channel blocker				
insulin		Diuretics				

Fasting. Yes.  No.

Regular monitoring of blood glucose? . Yes.  No.

Fasting blood glucose  HbA1c

Cholesterol  triglycerides  HDL  LDL   
VLDL

Creatinine  Na<sup>+</sup>  K<sup>+</sup>  Urea

WBC  Nitrophils  lymphocytes  HGB

Figure 3b: Questionnaire used in the study (page 2)

## Chapter III

### Results

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## 1. Baseline characteristics of study subjects

Baseline characteristics of study subjects, which included age, sex, ethnicity, height, weight, waist size, BMI, education, monthly income, Smoking habits, physical activity, duration of diabetes, type of diabetes, diet habits and water intake were recorded (Table 4).

Subjects with age ranges 20-29Y, 30-39Y, 40-49Y, 50-59Y and 60-69Y represented 6%, 11%, 22%, 47% and 14% respectively of whole study sample (Table 4). Females represented 28% of study sample; meanwhile males represented 72% of study sample (Table 4). Patients with North African ethnicity represented 91% of whole study sample, meanwhile patients with black ethnicity represented 9% of whole study sample (Table 4).

According to body measurements the mean  $\pm$  SEM (n) of height (cm), weight (kg) and waist size (cm) were  $170.47 \pm 0.91(100)$ ,  $84.80 \pm 1.9(100)$  and  $96.57 \pm 1.60(100)$  respectively of whole study sample (Table 4).

Subjects with BMI ( $\text{kg}/\text{m}^2$ ) ranges  $< 18.5$ , 18.5-24.9, 25-29.9 and 30-39 represented 3%, 17%, 30% and 50% respectively of whole study subject (Table 4).

Patients attended School at certain point of their lives represented 45% of study sample, patients gained higher education represented 32% of study sample and illiterate patients represented 23% of study sample (Table 4).

Patients with monthly income  $\leq 500$  LD represented 53% of whole study sample, the patients with monthly income 500-1000 LD represented 31% of study sample with patients have monthly income 1000-1500 LD represented 16% of study sample (Table 4).

Smokers represented 38% of the study sample; meanwhile non-smokers represented 62% of whole study sample (Table 4).

Patients who do physical activity regularly represented 27% of whole study sample but 73% of whole sample are not doing regular physical activity (Table 4)

Patients with diabetes duration of 1-5 years was 25%, 5-10 years was 51% and patients with disease duration more 10 years was 24% (Table 4).

Type1 diabetic patients represented 8% of whole study sample; meanwhile type 2 diabetic patients represented 92% of study sample (Table 4).

Subjects used to have fruits and/or vegetables represented 67% of whole study sample, and none of patients used to have a special diet (Table 3).

The results revealed that 24% of whole patients used to consume less than 1 liter of water per day, 69% of whole patients used to consume 1-2 liters of water per day and 7% of whole patients used to consume water more than 2 liters of water per day (Table 4).

**Table 4: Baseline characteristics of study subjects**

Characteristics	Mean $\pm$ S EM (n)	%
<b>Age (years)</b>		
20-29		6
30-39		11
40-49		22%
50-59		47%
60-69		14%
<b>Sex</b>		
Female		28%
Male		72%
<b>Ethnicity</b>		
North African		91%
Black		9%
<b>Body measurements</b>		
Height (cm)	170.47 $\pm$ 0.91 (100)	
Weight (kg)	84.80 $\pm$ 1.90 (100)	
Waist size (cm)	96.56 $\pm$ 1.60 (100)	
<b>BMI (kg/m<sup>2</sup>)</b>		
< 18.5		3%
18.5-24.9		17%
25-29.9		30%
30 - 39.9		50%
<b>Education</b>		
School attendant		45%
Higher education		32%
Illiterate		23%
<b>Monthly income (Libyan Dinar)</b>		
$\leq$ 500		53%
500-1000		31%
1000-1500		16%
<b>Smoking habit</b>		
No smoking		62%
Smoking		38%
<b>Physical activity</b>		
Do physical activity		27%
No physical activity		73%
<b>Duration of diabetes mellitus</b>		
1-5 years		25%
5-10years		51%
>10 years		24%
<b>Type of diabetes</b>		
Type I		8%
Type II		92%
<b>Diet habits</b>		
Fruits, vegetables intake		67%
Special diet		00%
<b>Water intake (Liters/day)</b>		
< 1		24%
1-2		69%
>2		7%

## 2. Family history of diabetes among study subjects

According to this study 63% of sample has got family history of diabetes while 37% were not (Figure 4). Out of whole diabetic patients with family history, 66.67% of patients have got family history related to mother, 19.05% of patients have got family history related to two parents, 11.11% of patients have got history family related to father and 3.17% of patients have got family history related to both parents together with brother or sister (Figure 5).

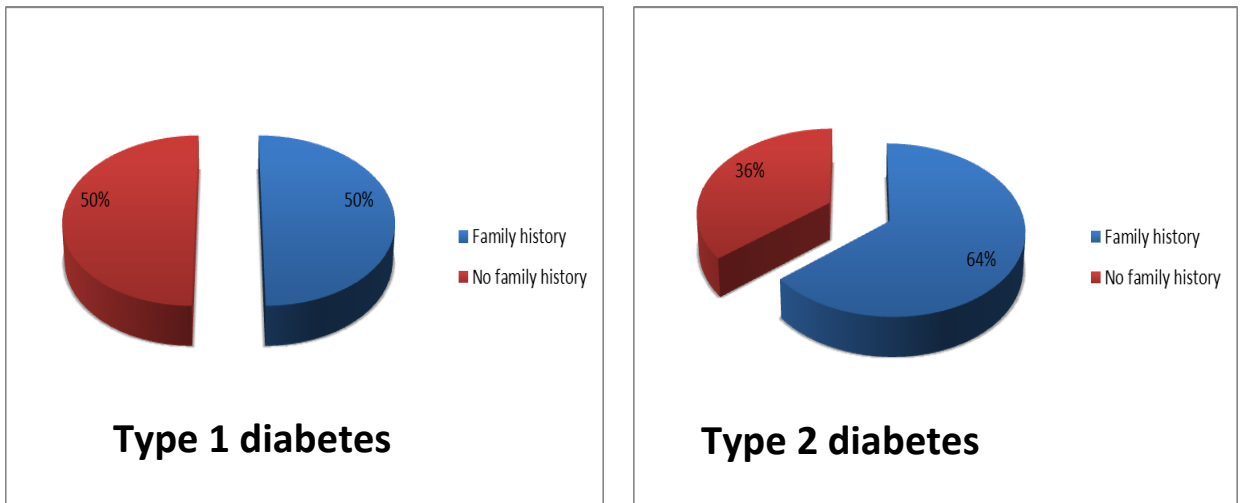


Figure 4: Diabetic patients and family history of the disease

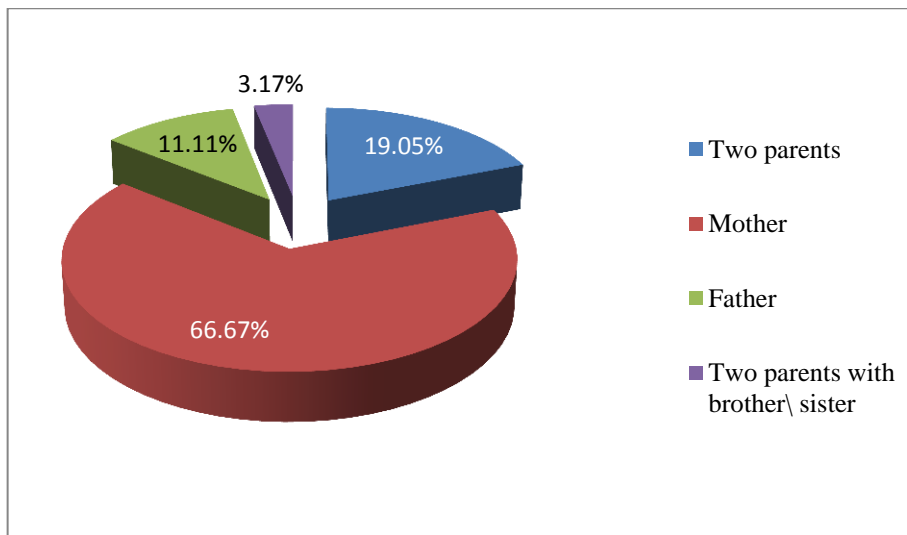


Figure 5: Diabetic patients and detailed family history of the disease

### 3. Risk factors & common symptoms

Weakness represented 76% of common symptoms among study sample (Figure 6). Depression & sleeplessness represented 69% of common symptoms among study sample (Figure 6). Hypertension represented 50% of risk factors among study sample (Figure 6). Muscle fatigue represented 38% of symptoms among study sample (Figure 6). Itching and nausea represented 29% & 15% respectively of common symptoms in study sample (Figure 6). Ischemic heart diseases (IHD), coma and kidney diseases represented 13%, 12% and 2% respectively of risk factors in study sample (Figure 6).

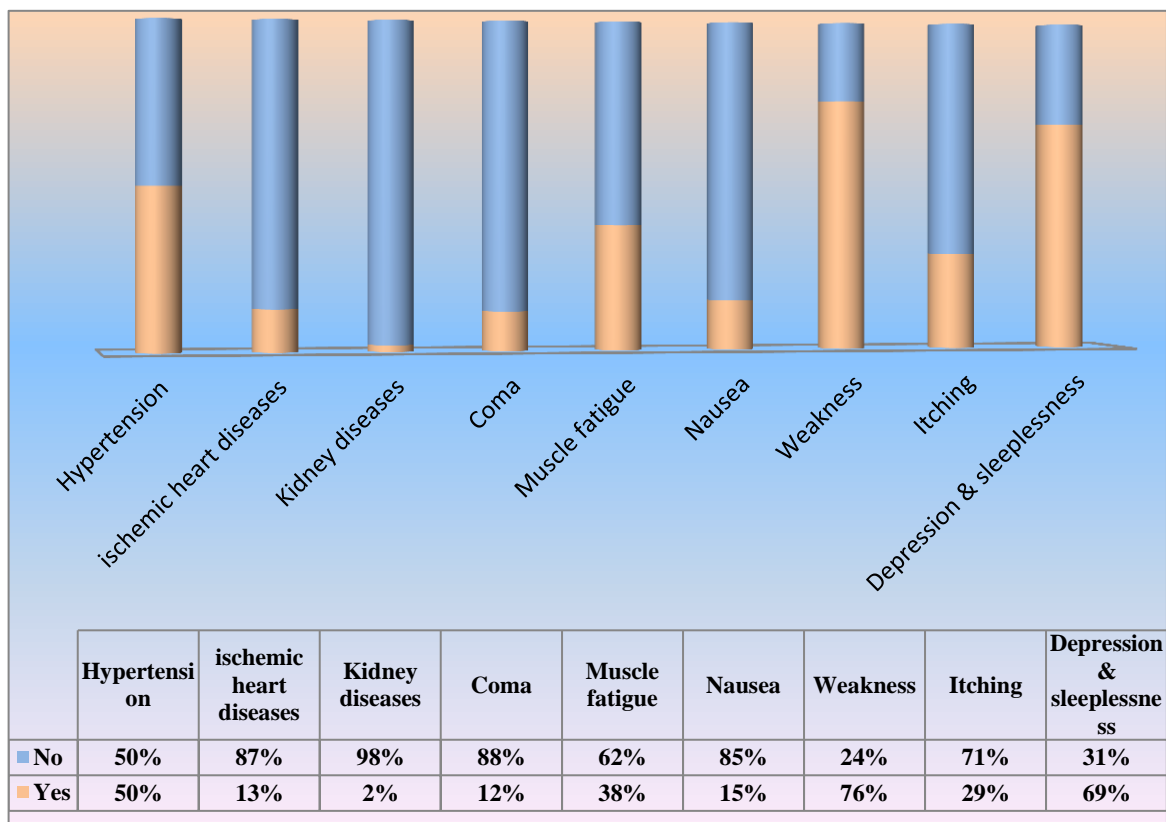


Figure 6: Risk factors and common symptoms among study subjects



#### 4. Drug (s) consumption

Patients used to adhere to drug treatment represented 83% of study sample, meanwhile 17% of patients admitted that they do not adhere to treatment (Figure 7). Patients taking only 1-2 drugs represented 23% of whole study sample; meanwhile patients taking more than 2 drugs represented 77% of whole study sample (Figure 8). Biguanides, sulfonylureas and insulin were used by 52%, 46% & 43% of study sample respectively (Figure 9). ACEIs & ARABs, diuretics and calcium channel blocker drugs were used by 34%, 18% and 8% respectively of study sample (Figure 9). Antihyperlipidimic drugs were used by 43% of study sample (Figure 9). Alternative medicines were used by 6% of study sample (Figure 9).

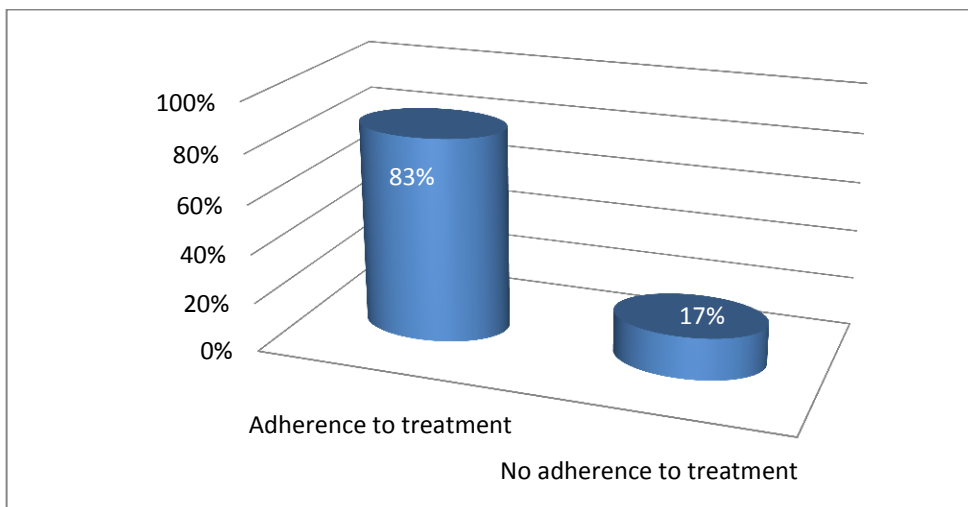


Figure 7: Adherence of diabetic patients to treatments

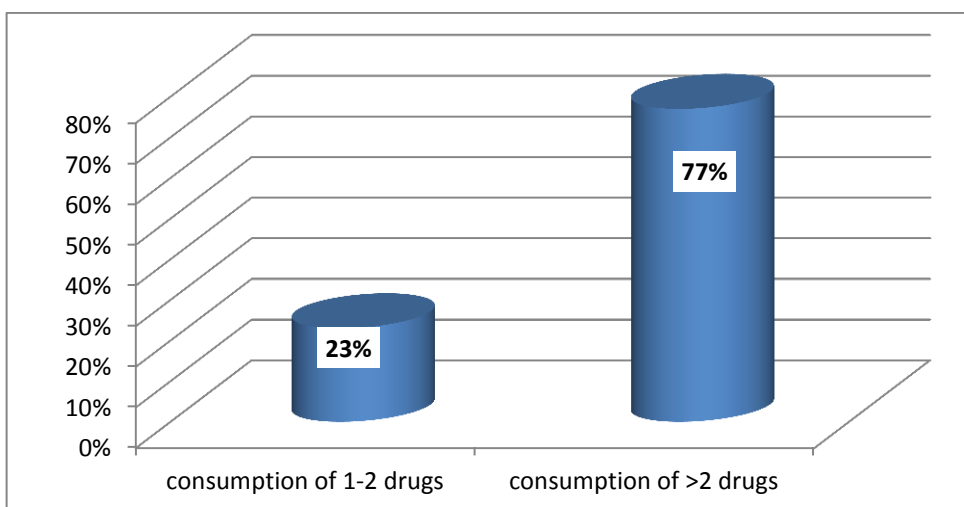
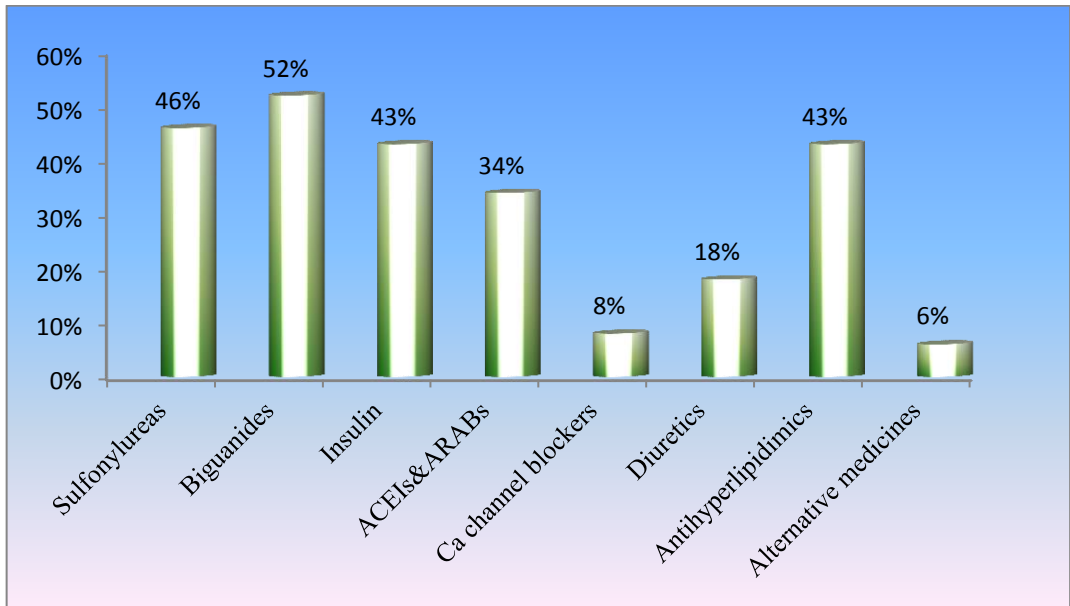


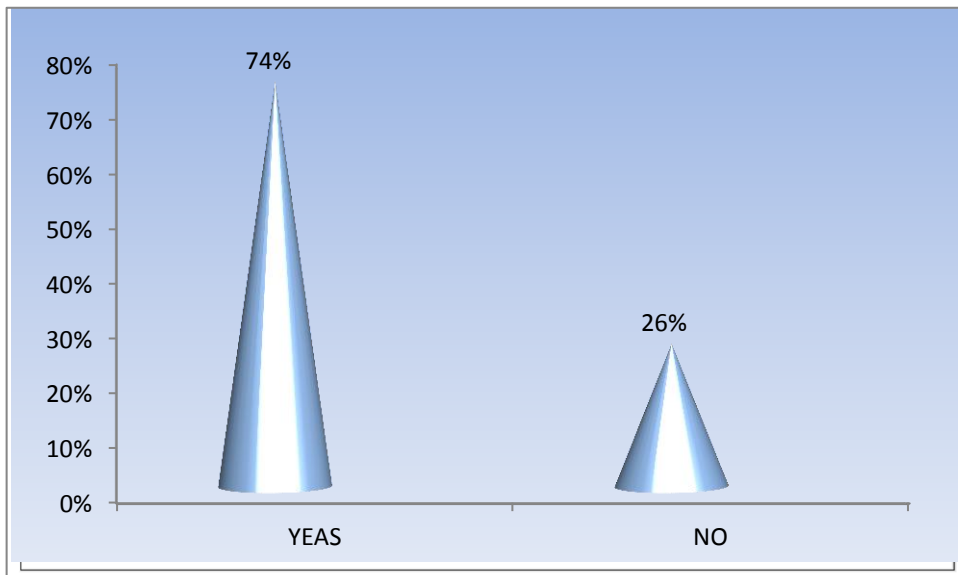
Figure 8: Number of drugs consumed by diabetic patients



**Figure 9: The most commonly used drugs by diabetic patients**

### 5. Regular monitoring of blood glucose level

Patients who were keen to regularly monitor their blood glucose level represented 74% of study sample, meanwhile 26% of patients admitted that they do not care to regularly monitor their blood glucose level (Figure 10).



**Figure 10: Regular monitoring of blood glucose level**

## 6. Clinical investigation tests

According to clinical investigation tests the results revealed that the Mean  $\pm$  SEM of cholesterol was  $209.95 \pm 5.75$  mg/dl, LDL was  $105.39 \pm 8.73$  mg/dl, FBS was  $201.21 \pm 7.22$  mg/dl, HbA1C was  $8.4 \pm 0.16\%$  which all showed slight differences to reference values. On the other hand the Mean  $\pm$  SEM of triglycerides, HDL, WBC, netrophil, lymphocytes, Hb, creatinine, Na, k and urea were  $194.33 \pm 10.11$  mg/dl,  $43.51 \pm 1.28$  mg/dl,  $8.7 \times 10^3/\text{ul} \pm 0.23$ ,  $60.9 \pm 1.80\%$ ,  $30.7 \pm 1.53\%$ ,  $13.17 \pm 0.18$  g/dl,  $1.12 \pm 0.1$  mg/dl,  $138.57 \pm 0.64$  mmol/L,  $4.17 \pm 0.08$  mmol/L and  $38.67 \pm 3.59$  mg/dl respectively and they did not show any differences to reference value (Table 5).

**Table 5: Clinical investigation tests**

Test	Reference value	Mean	SEM	n
Cholesterol	50 - 200 mg/dl	209.95	5.75	100
Triglycerides	40 - 200 mg/dl	194.33	10.11	100
HDL	40 - 55 mg/dl	43.51	1.28	100
LDL	<100 mg/dl	105.39	8.73	100
FBS	70 - 115 mg/dl	201.21	7.22	100
HbA1c	4 - 6 %	8.4	0.16	100
WBC	4 - 11 $10^3/\text{ul}$	8.7	0.23	100
Netrophil	54 - 62 %	60.9	1.80	100
Lymphocytes	25 - 33 %	30.7	1.53	100
Hb	13 - 17 g/dl	13.17	0.18	100
Creatinine	0.5 - 1.5 mg/dl	1.12	0.1	100
Na	135 - 145 mmol/L	138.57	0.64	100
K	3.5 - 5 mmol/L	4.17	0.08	100
Urea	10 - 50 mg/dl	38.67	3.59	100

HDL; High density lipoprotein, LDL; Low density lipoprotein, FBS; Fasting blood sugar, HbA1c; Glycated hemoglobin, WBC; White blood cell, Hb; Hemoglobin, Na; Sodium, K; Potassium.

# Chapter IV

## Discussion and conclusion

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## Discussion

This study examined the profile of diabetic patients in the Eastern region of Libya. The incidence of DM increased with age, which could be related to the pattern of physical activity of patient. The low incidence of DM in older patients may be because they are not keen to do regular monitoring of blood glucose level, and this could be due to many different social reasons.

This study showed that patients with North African ethnicity represented 91% of whole study sample, meanwhile patients with black ethnicity represented 9% of whole study sample. This is in contrast with previous study by Marshall and his colleagues, which revealed that type 2 diabetes is approximately twice as common in blacks and Hispanics as in non-Hispanic whites.<sup>44</sup> May be we should use more than 2 categories of ethnicity while classifying Libyan population. Using of either black or North African ethnicity as in this study, is not enough.

According to this study a higher incidence of diabetes in males (72%) compared to females (28%) was reported and this disagree with previous studies from India<sup>68,69,70</sup> Also the WHO reported that rise in blood glucose was 14.5% among males and 14.4% among females in Libya in 2008<sup>(5)</sup>. This discrepancy in results could be due to inhomogeneous study sample, which could be related to security situation especially in Benghazi city. Another factor for inhomogeneity of study sample could be that one of the study investigators is male and other is female and they worked separately but each interviewer could not interview except same sex patients visiting a specified clinic at a specified time.

Smoking as a risk factor was considered only for males. Noting that all females in our community admitted that they are non-smokers, and this is usually for social reasons. In this study smokers were 38% among whole sample, and this may be considered a relatively high percentage compared to a previous study.<sup>25</sup>

Regarding education the highest incidence was associated with patients who are school attendant (45%), the lowest with illiterate diabetic patients (23%) and this could be because of the fact that most of the illiterate patients should have job requiring physical exertion.

BMI gives important independent prediction of developing diabetes, a lot of studies used BMI independent predictor.<sup>70-73</sup> Current study showed that 80% of study sample are either overweight or obese.

The patients with low income represented (53%) of study sample. This is in concordance with previous study by Hamman.<sup>50</sup> The low income lead to life stress, and continued body

secretion of hormones such corticosteroids and epinephrine which all may influence insulin hormone.

Ecologic studies, suggest that NIDDM prevalence is consistently lower in populations with higher levels of habitual physical activity.<sup>47,48</sup> Despite evidence for the benefits of exercise, adherence to long-term exercise programs can vary between 10% and 80%, particularly in the long term.<sup>74</sup> Several prospective studies from western countries reported that physical activity was independent risk factor in development of diabetes.<sup>75,76</sup> Our study showed that only 27% of whole diabetic patients do physical activity.

Type 1 diabetic patients represented 8% of whole study sample in this study, this is similar to a report by American Diabetes Association, which revealed that type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide.<sup>17</sup> At the same time type 2 of diabetes in this study which represented 92% of study sample, agrees with study by González.<sup>18</sup>

Our study revealed that 67% of whole study sample servings vegetables and none of patients used to have special diet. In a 12-year prospective study in the USA, the risk of diabetes was significantly increased among men with 'Western' dietary pattern (characterized by higher consumption of red/processed meat, French fries, high-fat dairy products, refined grains, sweets, and desserts), compared to those having a 'prudent' dietary pattern comprising of fresh vegetables and fruits, fish, poultry, and whole grains. In addition to the fat that the risk was significantly greater among obese men.<sup>77</sup>

In our study 24% of diabetic patients used to consume < 1 liter of water per day and 69% of diabetic patients used to consume about 1-2 liters per day and the patients with water intake > 2 liters per day were only 7%. French cohort suggested that a low plain water intake may increase risk of new-onset hyperglycemia during a 9 years follow-up period.<sup>78</sup> We have to admit that most of the participate in this study did not know how much cups or liters of water do they should drink per day, and what is the importance of water to their health, and consequently most values of water intake reported in this study are approximate.

The present study showed that 63% of diabetic patients have family history of diabetes with, maternal history of diabetes to be a stronger risk factor compared to other family members history of diabetes. Studies reported relatively higher risk with maternal history of diabetes compared to paternal.<sup>79, 80</sup> In contrast, to our study some other studies revealed that the risk increased synergistically when both parents were diabetic.<sup>81</sup>

Diabetes is a leading cause of adult weakness, Lack of physical activity and high blood glucose can further worsen fatigue. Fatigue and tiredness can further contribute to weakness and decreased muscle strength.<sup>82</sup> Also, there is a strong relationship between depression and diabetes.<sup>83</sup> Depression has been associated with hyperglycemia and complications from diabetes.<sup>84</sup> Furthermore, depression in people with diabetes has been associated with socio-demographic lifestyle and clinical factors such as obesity and physical limitations.<sup>85</sup> The prevalence of depression is significantly higher in people with diabetes as compared to those without diabetes.<sup>86</sup> In a study conducted by Olvera et al. (2007) the prevalence of depression among a sample of 96 Latinas with diabetes was found to be approximately 32.3%.<sup>87</sup> Our study revealed high prevalence of weakness, fatigue, depression and sleeplessness with diabetic. Another study, conducted in 2000 showed that among diabetic patients 70.4% with hypertension.<sup>88</sup> This result is slightly higher than our results (50%). A study by Shima showed 46% of diabetic patients have hypertension and 19% had diabetic coma, while in this study 12% of Individuals with diabetes mellitus have an increased risk of CV disease and premature mortality.<sup>89-90</sup> Adherence and Compliance Adherence, as used in chronic disorders, was defined by the WHO as the extent to which a person's behavior with respect to taking medication. There are numerous reviews indicating the lack of adherence to treatment with one or more oral hyperglycemic agent. It has been demonstrated that there is an inverse relationship between taking a prescribed oral hyperglycemic agent and HbA1c level, with each 10% increase in oral hyperglycemic agent adherence associated with a decrease of 0.1% in HbA1c.<sup>91</sup> The prevalence of adherence to therapy for diabetes found in this study was 83% among study sample with 77% of them used to have more than two drugs. In this study diabetic patients who were keen to regularly monitor their blood glucose level represented 74% of study sample. This is comparable to previous studies from other places or countries.<sup>25</sup> According to clinical investigation tests results of this study revealed that cholesterol, LDL, FBS, HbA1C all showed only slight differences to reference values. A study by Issa and his colleagues in 2007 demonstrated a significantly higher level of plasma, LDL, VLDL and triglycerides and significantly decreases in plasma HDL observations in type 2 diabetes patients with IHD than type 2 patient without IHD.<sup>54</sup>

## **Conclusion**

High percentage of risk factors of DM including obesity, family history of diabetes, depression & hypertension requires a Libyan national policy for the surveillance, prevention and control of diabetes and its complications.



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