INTRODUCTION

Hypoglycemia is the most common and easily preventable endocrine emergency. With increasing incidence of diabetes and with various modalities of intensive control of blood glucose levels, there is always a risk of a proportional increase in the incidence of hypoglycemia ***(Holstein et al., 2003).***

Hypoglycemia is not a disease in itself; it is a sign of a health problem, whose importance lies in its effects upon brain function ***(Nordqvist, 2017).***

Hypoglycemia is usually defined as a plasma glucose level <70 mg/dL (3.9 mmol/L) ***(Desouza et al., 2010).***

Hypoglycemia is a true medical emergency which requires prompt recognition and treatment to prevent organ and brain damage. The spectrum of symptoms depends on duration and severity of hypoglycemia and varied from autonomic activation to behavioral changes to altered cognitive function to seizures or coma. The short and long term complications include neurologic damage, trauma, cardiovascular events and death ***(*Cryer PE*, 2009).***

Attempts made at intensive glycemic control invariably increases the risk of hypoglycemia. A six-fold increase in deaths due to diabetes has been attributed to patients

experiencing severe hypoglycemia in comparison to those not experiencing severe hypoglycemia. Repeated episodes of hypoglycemia can lead to impairment of the counter-regulatory system with the potential for development of hypoglycemia unawareness ***(Holman et al., 2008).***

The short- and long-term complications of diabetes related hypoglycemia include precipitation of acute cerebrovascular disease, myocardial infarction, neurocognitive dysfunction, retinal cell death and loss of vision in addition to health-related quality of life issues pertaining to sleep, driving, employment, recreational activities involving exercise and travel ***(Sanjay Kalra et al., 2013).***

Counter-regulatory response to hypoglycemia includes inhibition of the endogenous insulin secretion and stimulation of glucagon, catecholamines (nor epinephrine, epinephrine), cortisol and growth hormone secretion, which all together stimulate hepatic glucose production and cut down glucose utilization in peripheral tissues, increasing in this way plasma glucose levels ***(de Galan et al., 2006).***

Hypoglycemi can be a dangerous condition that happens in people with diabetes who take medicines that increase insulin levels in the body. Taking too much medication, skipping meals, eating less than normal or exercising more than usual can lead to low blood sugar for these individuals ***(Fadini et al., 2009).***

Hypoglycemic severity was categorized as 1) mild (little or no interruption of activities and no assistance needed to manage symptoms); 2) moderate (some interruption of activities and no assistance needed to manage symptoms); 3) severe (needed the assistance of others to manage symptoms) ***(The American Diabetes Association Workgroup on Hypoglycemia, 2005).***

Hypoglycemia can be diagnosed by Whipple's triad which consists of Symptoms consistent with hypoglycemia, a low plasma glucose concentration measured by an accurate method, and relief of the symptoms when the plasma glucose level is raised ***(Henderson et al., 2007).***

Hypoglycemia unawareness (HU) is defined at the onset of neuroglycopenia before the appearance of autonomic warning symptoms. It is a major limitation to achieving tight diabetes and reduced quality of life. Recurrent hypoglycemia has been shown to reduce the glucose level that precipitates the counter-regulatory response necessary to restore euglycemia during a subsequent episode of hypoglycemia ***(Briscoe et al., 2006).***

In the context of comprehensive treatment, including weight, blood pressure and blood cholesterol control among other measures, glycemic control makes a difference for people with diabetes. Partial glycemic control reduces

microvascular complications (retinopathy, nephropathy, and neuropathy). Follow-up of patient's diabetes suggests that an earlier period of partial glycemic control may also reduce macrovascular complications. Clearly, maintenance of euglycemia over a lifetime of diabetes would be in the best interest of people with diabetes if that could be accomplished safely ***(UK Prospective Diabetes Study).***

The overall objective of type 2 diabetes's management is to achieve and maintain blood glucose control and reduce the risk of long-term complications. Many studies have shown that modern management with intensive glycemic control can limit, delayed or even prevent the chronic complications of diabetes. However this intensive diabetes treatment could be associated with an increased risk of hypoglycemia ***(Donnelly et al., 2005).***

Aim of the Work

The aim of the study is to:

1. Measure the frequency of hypoglycemic attacks in type 2 diabetic patients in clinic based study.
2. Correlate the attacks of hypoglycemia with treatment regimens and duration of the diabetes.
3. Identify the degree of adherence to treatment among diabetic patients.

Chapter (1): Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus:

Type II DM is characterized by chronic hyperglycemia secondary to defects in insulin secretion, action or both ***(Nayak and Roberts, 2011).***

Type II DM is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency with disturbances of carbohydrate, fat, and protein metabolism ***(Kumar et al., 2015).***

Epidemiology:

The prevalence of diabetes has reached epidemic proportions in most populations. According to the UN World Health Organization (WHO) more than 220 million people worldwide have diabetes, from which more than 70% live in low- and middle income countries. It is expected that the number of diabetic subjects grows to 366 million by 2030. Epidemiologic evidences suggest that unless effective preventive measures are implemented the global prevalence will continue to rise ***(Alberti et al., 2007).***

The global burden:

- The greatest number of people with diabetes is between 40 to 59 years of age.
- 183 million people (50%) with diabetes are undiagnosed
- Diabetes caused 4.6 million deaths in 2011.
- Diabetes caused at least 465 billion dollars in healthcare expenditures in 2011; 11% of total healthcare expenditures in adults (20-79 years).

(IDF, 2011).

Prevalence of DM in Egypt:

In Egypt the prevalence of diabetes was about 7.30 million in 2011 and expected to be 12.40 million in 2030 ***(IDF Diabetes Atlas, 2011).***

Table (1): Prevalence of diabetes in 2011 and 2030.

Year	Country/territory	Millions
2011	1- China	90.0
	2- India	61.30
	3- United States of America	23.70
	4- Russian Federation	12.60
	5- Brazil	12.40
	6- Japan	10.70
	7- Mexico	10.30
	8- Bangladesh	8.40
	9- Egypt	**7.30**
	1. Indonesia	7.30
2030	1- China	129.70
	2- India	101.20
	3- United states of America	29.60
	4- Brazil	19.60
	5- Bangladesh	16.80
	6- Mexico	16.40
	7- Russian federation	14.10
	8- Egypt	**12.40**
	9- Indonesia	11.80
	10- Pakistan	11.40

(IDF Diabetes Atlas, 2011)

Table (2): Risk factors for T2DM:

Non modifiable risk factors	Modifiable risk factors
1- Family history. 2- Race 3- Age	1- Weight 2- Fat distribution 3- Inactivity 4- Prediabetes 5- Gestational diabetes 6- Dyslipedemia 7- Polycystic ovary syndrome 8- Acanthosisnigricans 9- Depression or stress 10- Smoking 11- Sleep disorders 12- Cardiovascular disease

(Mayo, 2012)

Criteria for testing for diabetes in asymptomatic individuals:

Testing should be considered in all adults who are overweight (BMI ≥ 25kg/m2) and have additional risk factor:

- Physical inactivity.
- First degree relative with diabetes.
- High risk race/ethnicity.
- Women who delivered a baby weighting more than 4.5kg or were diagnosed with gestational diabetes.
- Hypertension≥140/90 or on therapy of Hypertension.
- HDL cholesterol <35mg/dl. And or TG >250 mg/dl.
- Women with PCO syndrome.
- HBA1C ≥ 5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing.
- Other clinical condition associated with insulin resistance.
- History of cardio-vascular disease (C.V.D).

In the absence of the above criteria, testing for diabetes should begin at age of 45 and if the above results are normal, testing should be repeated at least at 3 year interval, with consideration of more frequent testing depending on initial results and risk status ***(ADA, 2012).***

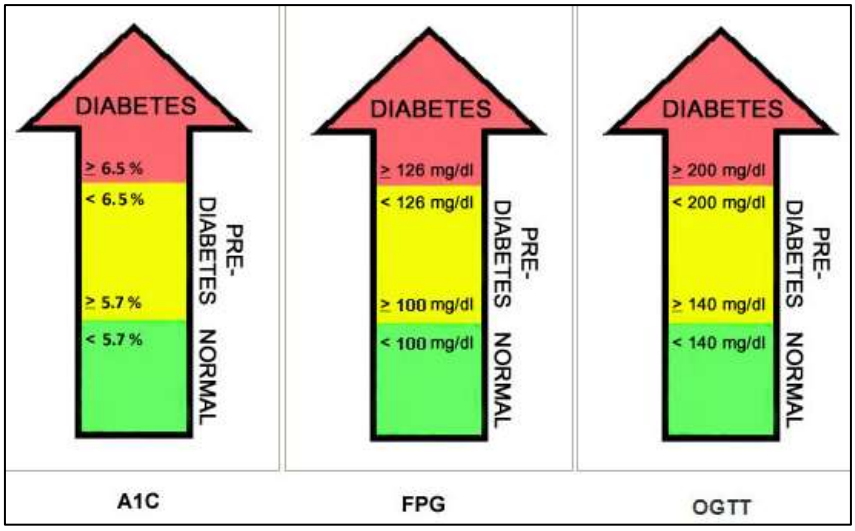

Figure (1): Diagnosis of diabetes mellitus ***(ADA, 2012).***

Patients with fasting plasma glucose levels from 100 to 125 mg/dl (5.6 to 6.9 mmol/l) are considered to have impaired fasting plasma glucose. Patients with plasma glucose at or above 140 mg/dl (7.8 mmol/l), but not over 200 mg/dl (11.1 mmol/l), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus and cardiovascular disease ***(Santaguida et al., 2008).***

The revised criteria for the diagnosis of diabetes are shown in **Table 3**. Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given in **Table 3** ***(ADA, 2012).***

Table (3): Criteria for the diagnosis of diabetes mellitus.

In a patient with classic symptoms of hyperglycemia or a random plasma glucose ≥ 200mg/dl.
With
FPG≥126mg/dl.Fasting is defined as no caloric intake for at least 8 hours.
Or
2hrPPPG ≥ 200mg/dl. During an OGTT. Should be performed as described by the WHO, using a glucose load containing 75gm anhydrous glucose.
Or
A1C ≥ 6.5. Should be performed in a laboratory using a method that is NGSP certified

(ADA, 2012)

Complications of T2DM:

The complications of T2DM are far, less common and less severe in people who have well-controlled blood sugar levels. Uncontrolled blood sugar causes several problems that may lead to sudden and / or long term diseases, so complications are divided into acute and chronic complications **Table 4** ***(Rich, 2009).***

Table (4): Complication of T2DM

Acute Complications	Chronic complications	
	Macro-angiopathy	Micro-angiopathy
Diabetic ketoacidosis	Coronary artery disease	Nephropathy
hyperosmolar Hyperglycemia	Myonecrosis	Retinopathy
Hypoglycemic coma	PVD	Polyneuropathy
Diabetic coma	Stroke	
Respiratory infections		
Periodontal disease		

(Rich, 2009)

Acute complications:

1. Diabetic coma

Diabetic coma is a reversible form of coma found in people with T2DM. It is a medical emergency and three different types of diabetic coma are identified: severe diabetic hypoglycemia, Diabetic ketoacidosis, and Hyperosmolar non-ketotic coma. Treatment depends upon the underlying cause ***(Richard and James, 2010).***

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute and dangerous complication that is always a medical emergency. It happens predominantly in those with type 1 diabetes, but it can occur in those with T2DM under certain circumstances. Low insulin levels cause the liver to turn fatty acid to ketone for fuel (i.e., ketosis); ketone bodies are intermediate substrates in that metabolic sequence. Elevated levels of ketone bodies in the blood decrease the blood's pH, leading to DKA.

DKA may be the first symptom of previously undiagnosed diabetes, but it may also occur in people known to have diabetes as a result of a variety of causes, such as inter current illness or poor compliance with insulin therapy. Vomiting, dehydration, deep gasping breathing,

confusion and occasionally coma are typical symptoms. Urine analysis will reveal significant levels of ketone bodies. Treatment is: intravenous fluids, insulin and administration of potassium and sodium ***(Eledrisi et al., 2011).***

Hyperosmolar hyperglycemic state (HHS)

Hyperosmolar hyperglycemic state (HHS) is one of two serious metabolic derangements that occurs in patients with diabetes mellitus (DM) and can be a life-threatening emergency. HHS most commonly occurs in patients with type II DM who have other concomitant illness that leads to reduced fluid intake. Infection is the most common preceding illness, but many other conditions can cause altered mentation, dehydration, or both. HHS is characterized by: hyperglycemia (Plasma glucose level of 600 mg/dl or greater), hyper osmolarity (serum osmolality of 320 mosm/kg or greater), and dehydration without significant ketoacidosis. Treatment is: plenty of intravenous fluids, insulin, potassium and sodium given as soon as possible ***(Bhowmick et al., 2015).***

Hypoglycemic coma

Hypoglycemia (low blood sugar) levels below 3.9 mmol/L (70 mg/dL), low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis ***(Benjamin et al., 2014).***

2. Respiratory infections

The immune response is impaired in individuals with T2DM. Cellular studies have shown that hyperglycemia both reduces the function of immune cells and increases inflammation. The vascular effects of diabetes also tend to alter lung function, all of which leads to an increase in susceptibility to respiratory infections ***(Connie and Hsia, 2013).***

3. Periodontal disease

Diabetes is associated with periodontal disease (gum disease) and may make diabetes more difficult to treat. Gum disease is frequently related to bacterial infection. A number of trials have found improved blood sugar levels in type 2 diabetics who have undergone periodontal treatment ***(Lakschevitz et al., 2011).***

Macro vascular complications:

1- Coronary artery disease

It is also known as "atherosclerotic heart disease" or "ischemic heart disease". The disease is caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and reduces blood flow to the heart presented by chest pain "angina". Pathologically, it occurs when part of the smooth, elastic lining inside a

coronary artery develops atherosclerosis under effect of diabetes making the artery's lining becomes hardened, stiffened, and swollen with all sorts of "gunge" - including calcium deposits, fatty deposits, and abnormal inflammatory cells - to form the plaque ***(Lanza, 2007).***

2- Diabetic myonecrosis

It is a rare complication of diabetes, with mean age of onset since diagnosis of diabetes is fifteen years and female: male ratio is 1.3: 1. It is infarction of muscle tissue, usually in the thigh due to arteriosclerosis of obliterans supplying the muscles ***(Wintz et al., 2011).***

3- Peripheral vascular disease

PVD is a term used to refer to atherosclerotic blockages found in the lower extremity. PVD can result from atherosclerosis, inflammatory processes leading to stenosis, embolism, or thrombus formation. It causes either acute or chronic ischemia (lack of blood supply). Diabetes causes between two and four times increased risk of PVD by causing endothelial and smooth muscle cell dysfunction in peripheral arteries and the risk of developing lower extremity peripheral arterial disease is proportional to the severity and duration of diabetes ***(Weiss and Sumpio, 2011).***