INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone ***(Kharroubi and Darwish, 2015).***

Diabetes is one of the most common diseases that affect children and if not detected during early childhood, the disease can have deadly consequences or result in serious damage to the brain, so every parent, teacher; doctor involved in child care should be familiar with the warning signs and be alert to the threat ***(Rohde et al., 2015)***.

Diabetes is a chronic and progressive syndrome commonly associated with several neuropsychiatric co-morbidities, of which depression is the most studied ***(Zanoveli et al., 2016).***

Type 1 diabetes is a risk factor for the development of psychiatric disorders in children. A study of children with diabetes found that one third had psychiatric disorders, most involving internalizing symptoms; other studies have shown that the depression goes along with the poor glycemic control ***(Khandelwal et al., 2016).***

Depression is a serious illness that can affect nearly every part of a young person's life and significantly impact his or her family. It can disrupt relationships among family members and friends, harm school performance and limit other educational opportunities**.** It can lead to other health problems through its effects on eating, sleeping, and physical activity ***(Kusumakar et al., 2015)***.

The prevalence of depression is about two or three times higher in diabetic patients compared to the general population. It is believed that the diabetes - depression relation may be bidirectional, i.e., the depression can lead to diabetes and conversely diabetes could facilitate the emergence of depression ***(Chen et al., 2016).***

Depression is one of the most neglected symptoms in diabetic patients and is directly linked with lowering of quality of life ***(Bădescu et al., 2016).***

AIM OF THE WORK

The aim of the study is to detect depression disorder among adolescents with type 1 Diabetes Mellitus and determine the risk factors and relation to the glycemic control.

Chapter 1

TYPE 1 DIABETES IN CHILDREN

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidney, nerves, heart, and blood vessels ***(ISPAD, 2018).***

The classical symptoms of diabetes are polyuria, polydepsia, and polyphagia ***(Cooke and Plotnick, 2015).*** The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic Beta-cell damage (type 1 DM), and those that are consequence of insulin resistance occurring at the level of skeletal muscles, liver, and adipose tissue with various degrees of beta-cell impairment (type 2 DM) ***(Alemzadeh and Ali, 2011).***

Prevalence and incidence of T1dm

WHO estimates that more than 180 million people worldwide have diabetes; this number is likely to more than double by 2030; about 10% have T1DM ***(Jensen et al., 2012).***

Type I diabetes mellitus (T1DM) is the most common metabolic disorder in children. It constitutes 5-10 % of the total worldwide diabetes cases ***(Daneman, 2006),*** showing an annual increase of 3 % per year ***(DIAMOND Project Group, 2006).***

In an Egyptian study of retrospective design performed in the Delta region, age adjusted incidence of T1DM in the years 1996, 2006 and 2011 was 0.7, 2.0 and 3.1 cases/100000 accounting for a cumulative prevalence of 1.9, 15.5 and 26.8 cases /100000 respectively ***(El-Ziny et al., 2014).***

Role of Genetics in Disease Progression

Genetic determinants play a role in the susceptibility to DM1, although the mode of inheritance is complex and multigenic. Siblings or offspring of patients with diabetes have a risk of 2% to 8% for the development of diabetes; an identical twin has a 30% to 50% risk ***(Stankov et al., 2013)***.

The human leukocyte antigen (HLA) region on chromosome 6 provides the strongest determinant of susceptibility, accounting for approximately 40% of familial inheritance of DM1. Specific (HLA DR3 and HLA DR4) increase the risk of developing DM1, whereas other specific HLA alleles exert a protective effect ***(Polychronakos and Lirl, 2012)***.

More than 90% of children with DM1 possess HLA DR3 alleles, HLA DR4 alleles, or both.The insulin gene region variable number tandem repeat on chromosome 11 is also linked to DM1 susceptibility ***(Wahlberg et al., 2015)***.

There is evidence for association, beyond HLA, of more than 100 other loci with DM1. Genetic factors do not fully

account for susceptibility to DM1; environmental factors also play a role ***(Gillespie et al., 2014)***.

Classification:

Table (1): Classification of diabetes

I. Type 1
β-cell destruction, usually leading to absolute insulin deficiency
- A. Autoimmune
- B. Idiopathic

II. Type 2
May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Genetic defects of β-cell function
- Chromosome 12, HNF-1α (MODY3)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 20, HNF-4α (MODY1)
- Chromosome 13, insulin promoter factor (IPF)-1 (MODY4)
- Chromosome 17, HNF-1β (MODY5)
- Chromosome 2, *NeuroD1* (MODY6)
- Mitochondrial DNA mutation
- Chromosome 11, *KCNJ11* (Kir6.2), *ABCC8* [sulphonylurea receptor 1 (SUR1)]
- Others

B. Genetic defects in insulin action
- Type A insulin resistance
- Leprechaunism
- Rabson–Mendenhall syndrome
- Lipoatrophic diabetes
- Others

C. Diseases of the exocrine pancreas
- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy
- Others

D. Endocrinopathies
- Acromegaly
- Cushing syndrome
- Glucagonoma
- Phaeochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma
- Others

E. Drug or chemical induced
- Vacor
- Pentamidine
- Nicotinic acid
- Glucocorticoids
- Thyroid hormone
- Diazoxide
- β-adrenergic agonists
- Thiazides
- Dilantin
- α-Interferon
- Others

F. Infections
- Congenital rubella
- Cytomegalovirus
- Coxsackie B4
- Others

G. Uncommon forms of immune-mediated diabetes
- 'Stiff-man' syndrome
- Anti-insulin receptor antibodies
- Autoimmune polyendocrine syndrome deficiencies I and II
- Others

H. Other genetic syndromes sometimes associated with diabetes
- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome
- Wolfram's syndrome
- Friedreich's ataxia
- Huntington's chorea
- Laurence–Moon–Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader–Willi syndrome
- Others

IV. Gestational diabetes

HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young.

The vast majorities of cases with diabetes fall into two etiopathogenetic categories; type 1 and type 2 diabetes mellitus ***(ISPAD, 2018)***.

Table (2): Clinical characteristics of type 1 diabetes, type 2 diabetes and Monogenic diabetes in children and adolescents

Characteristics	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Clinical presentation	6 months to young Adulthood	Usually pubertal (or later)	Often post pubertal except GlucoKinase and neonatal diabetes
Association Autoimmunity Ketosis Obesity Acanthosis nigricans	Yes Common Population Frequency No	No Uncommon Increased Frequency Yes	No Common in neonatal diabetes, Rare in other form Population Frequency No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10%	?1-3%
Parent with diabetes 2	2-4%	80%	90%

(ADA, 2018)

Pathogenesis of T1DM

T1DM is an autoimmune disease with characteristic loss of insulin-producing pancreatic P-cells. The pathogenesis is multifactorial where genetic susceptibility and environmental triggers interact together to produce a series of pathological

processes ***(Anaya, 2014).*** Adaptive immunoregulatory T cells contribute to the modulation of the development and evolution of T1DM ***(Ferretti and La Cava, 2016).***

The autoimmune hypothesis of T1DM is supported by the co-existence of other autoimmune diseases in association with T1DM including autoimmune thyroiditis, Addison's disease, autoimmune gastritis and/or pernicious anemia and celiac disease (CD) ***(Kakleas et al., 2015).***

Insulitis in addition to P-cell autoantibodies are the mainstay of pancreatic autoimmunity in children with T1DM ***(Todd, 2015).*** In fact, one or more P-cell autoantibodies is present in approximately 90% of children with new-onset with T1DM ***(Atkinson et al., 2014).***

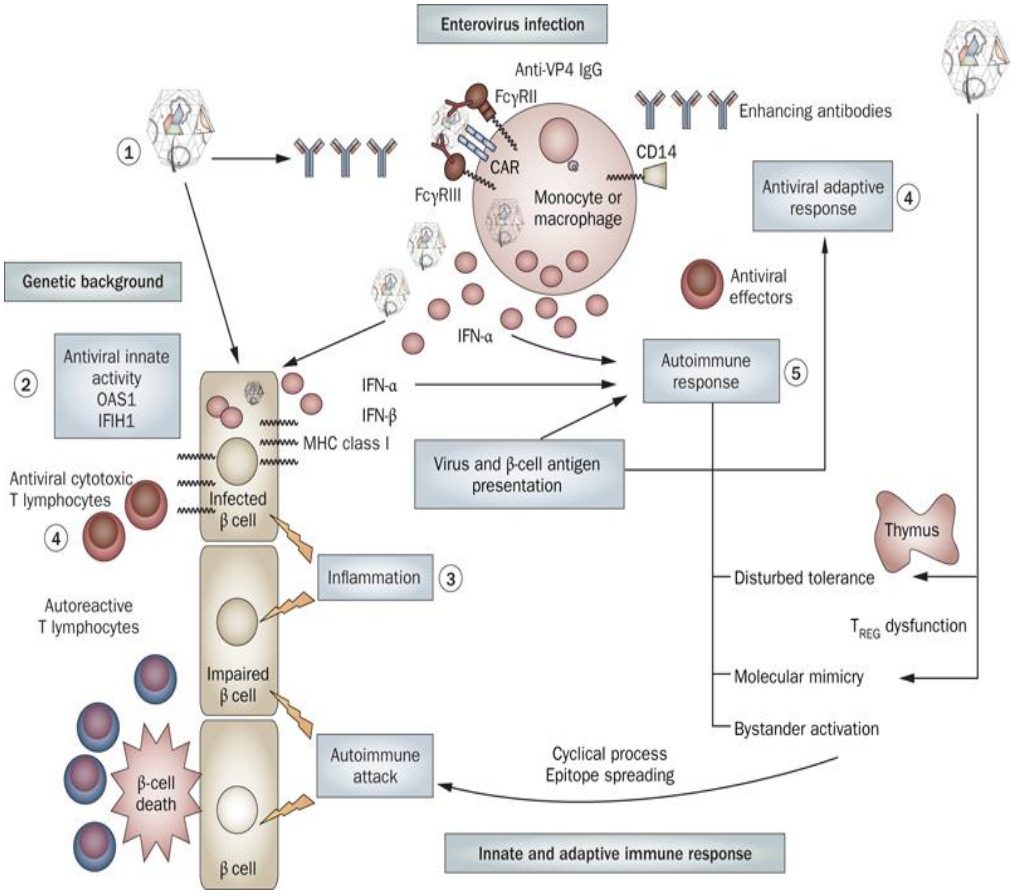

Figure (1): Pathogenesis of T1DM: Autoantibodies against islet antigens appear in the circulation during the autoantibody-positive phase. Later, autoreactive T cells proliferate and infiltrate the islets causing beta cell death. During the first years of the diabetic period, C-peptide might still be detectable as some beta cells manage to survive the immune attack ***(Christoffersson et al., 2016***).

Subtypes of Type 1 diabetes:

Type 1a (The autoimmune form):

This form of diabetes, which accounts for only 5-10% of those with diabetes, previously known insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results

from a cellular-mediated autoimmune destruction of pancreatic Beta-cells representing about 90% of type 1 cases in Europe. The presence of other autoimmune disorders is highly raised ***(ADA, 2018).***

Type 1b (the idiopathic form):

The cause of insulin deficiency is not related to autoimmunity and it remains undefined. These cases are categorized as type 1b or idiopathic type 1DM and are relatively more common in African and Asian population. This category is heterogeneous, may be caused by different mechanisms in different population, and remain poorly understood at this time ***(Kitabchi et al., 2016).*** Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for beta-cell autoimmunity, and is not HLA associated ***(ADA, 2018).***

Type 1c:

It is the fulminant type 1 diabetes mellitus (FT1DM), it was first reported by ***Hanafusa et al. (2014)*** and it is a unique subtype of diabetes. It is characterized by a short clinical history, before the first acute metabolic decompensation with impairment of beta and alpha cells of pancreatic islet and no autoimmune etiology ***(Nobuko et al., 2014).***

Diagnosis of T1DM:

Diagnosis of DM in children can be established on the criteria described in table 3 ***(Jefferies et al., 2014).*** Children with T1DM typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with DKA ***(Dykewicz et al., 2014).***

T1DM often develops suddenly and can produce symptoms such as polydipsia, polyuria, enuresis, lack of energy, extreme tiredness, polyphagia, sudden weight loss, slow-healing wounds, recurrent infections and blurred vision ***(Kharroubi and Darwish, 2015).***

Table (3): Criteria for the diagnosis of diabetes mellitus ***(American Diabetes Association, 2018).***

i. Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration >11.1 mmol/L (200 mg/dL) or
ii. Fasting plasma glucose >7.0 mmol/L (>126mg/dL). Fasting is defined as no caloric intake for at least 8h* or
iii. Two hour post load glucose >11.1 mmol/L (>200 mg/dL) during an OGTT*.
The test should bo performed using a glucose load containing the equivalent ol75g anhydrous glucose dissolved in water or 1.75g/kg of body weight to a maximum of 75 g or
1. HbA1c >6.5%t
* The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT] assay

(ADA, 2018)

Complications of T1DM

(I) Acute complications

1- Diabetic ketoacidosis (DKA):

Diabetic ketoacidosis (DKA) is a common presentation of type I diabetes mellitus to the emergency departments ***(Dabelea D et al., 2014).*** It is one of the most serious acute complications of type 1 diabetes mellitus (T1DM) and the leading cause of morbidity and mortality in children with T1DM ***(Atkilt et al., 2017).*** It is caused by severe insulin deficiency leading to hyperglycaemia ***(Glaser et al., 2014).***

2- Hypoglycemia:

As a result of low glucose levels, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progression to inability to seek help and seizures or coma (severe hypoglycemia) ***(Alemzadeh and Ali, 2011).***

3- Hyperosmolar non-ketotic coma

Is clinically defined by the presence of relative insulin deficiency and hyperglycemia, usually >1,000 mg/dl with associated elevated serum osmolality (>300 mosm/kg), dehydration, and stupor, progressing to coma if uncorrected, without the presence of ketosis or acidosis ***(Anil Bhansali, 2017).***

(II) Chronic complications:

Chronic complications can classifed into microvascular and macrovascular:

{A} Macrovascular complications

T1DM patients have increased risk of cardiovascular morbidity including coronary artery disease. This is attributed to the associated risk factor prevalent in those patients e.g. hypertension and dyslipidemia ***(Fowler, 2014).***

{B} Microvascular complications:

They include diabetic retinopathy, nephropathy and neuropathy. Risk factors for the development of micro-vascular complications:

a. Young age at the onset of the diabetes.
b. Long duration of diabetes.
c. Poor glycemic control**.**
d. Family history of diabetic complications.
e. Higher body mass index (BMI).
f. Smoking.
g. Abnormal lipid metabolism, weight and BMI.
h. Hypertension.
i. Sedentary life style.

(Chiarelli et al., 2014)

A1- Diabetic retinopathy

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for ~ 10,000 new cases of blindness every year in the United States alone ***(Rao et al., 2017).*** The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia ***(Ponnalagu et al., 2017).***

A2- Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" ***(ADA, 2018).***

As with other microvascular complications, risk of developing diabetic neuropathy is depend on both severity and duration of hyperglycemia, and some individuals may possess some genetic factors ***(Kordonouri et al., 2015).***

A3- Diabetic nephropathy

Diabetic nephropathy is currently the leading cause of end-stage renal disease. Despite optimal management, DN is still a major contributor to morbidity and mortality of diabetic patient's worldwide ***(Tepe et al., 2015).***

Management of type 1 diabetes:

1 - Education:

According to ***ISPAD Clinical Practice Consensus Guidelines (2018)***, education is the key to successful management of diabetes. There is evidence that educational interventions in childhood and adolescent diabetes have a beneficial effect on glycemic control and on psychosocial outcomes (***ISPAD, 2018)***.

2 - Diet:

One of the first steps in managing type 1 DM is diet control. According to ADA policy, dietary treatment is based upon nutritional assessment and treatment goals ***(ADA, 2018).*** Dietary recommendations should take into account the patient's eating habits and lifestyle ***(Ahmedani et al., 2012).***

3- Exercise:

Exercise might greatly benefit many patients with diabetes by improving their metabolic profile, dyslipidemia, aiding in their weight loss and maintaining their blood pressure ***(Haider et al., 2006)***.Exercise improves glycemic control by reducing HbA1c values and is dispensable component in the medical treatment of patients with T1DM as it improves glycemic control and decreases cardiovascular risk factors among them ***(Salem et al., 2010).***