INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and/or failure of various organs ***(ADA, 2005).*** Type 1 diabetes is a multifactorial chronic disease in which there is selective destruction of β cells due to an autimmune process ***(Pick up and Williams, 2003).***

Adiponectin is a member of a group of adipose secreted proteins, sometimes described as adipocytokines. Adiponectin is a plasma protein that has been discovered few years ago. It is produced exclusively and abundantly in adipose tissue and circulates at relatively high concentration ***(Esposito et al., 2003).*** Adiponectin has a great metabolic effects including enhancement of of insulin sensitivity, reduction of hepatic glucose production and decreasing gluconeogenesis ***(Pankowska and Szalecki, 2005).*** In addition, plasma adiponectin levels were found to be negatively correlated with body mass index (BMI) and fat content suggesting that fat mass may exert a negative feedback on adiponectin production ***(Aygun et al., 2006).***

The circulating concentrations of adipocytokines are abnormal in type 1 diabetic children. The direction of change differs according to cytokine, pubertal development; in addition to insulin therapy and glycemic control ***(Celi et al., 2006).***

The relationship between serum adiponectin concentration and pancreatic β cell function is a significant negative modulator for circulating adiponectin in diabetic patients and support the presence of adipoinsular axis ***(Furuta et al., 2006).***

AIM OF THE WORK

To determine the influence of type 1 DM in adolescent girls on circulating levels of adiponectin and to study the relation between adiponectin level and glycemic control.

DIABETES MELLITUS

Definition:

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues. If ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly ***(American Diabetes Association, 2014).***

Type 1 diabetes mellitus (type 1DM), one of the most common chronic diseases in childhood, is caused by insulin deficiency following destruction of the insulin-producing pancreatic beta cells. It most commonly presents in childhood, but one-fourth of cases are diagnosed in adults. Type 1DM remains the most common form of diabetes in childhood, accounting for approximately two-thirds of new diagnoses of diabetes in patients≤ 19 years of age in the United States, despite the increasing rate of type 2diabetes ***(American Diabetes Association, 2013).***

Classification of diabetes mellitus:

Table (1): Etiologic classification of diabetes mellitus:

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A. Genetic defects of β-cell function

- MODY 3 (Chromosome 12, HNF-1α)
- MODY 1 (Chromosome 20, HNF-4α)
- MODY 2 (Chromosome 7, glucokinase)
- Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, *NeuroD1*; MODY 7: Chromosome 9, carboxyl ester lipase)
- Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
- Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β-cell K_{ATP} channel)
- Mitochondrial DNA
- 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
- Hemochromatosis
- Fibrocalculous pancreatopathy
- Others

D. Endocrinopathies

- Acromegaly
- Cushing's syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma
- Others

E. Drug or chemical induced

- Vacor
- Pentamidine
- Nicotinic acid
- Glucocorticoids
- Thyroid hormone
- Diazoxide
- β-Adrenergic agonists

- Thiazides
- Dilantin
- γ-Interferon
- Others

F. Infections

- Congenital rubella
- Cytomegalovirus
- Others

G. Uncommon forms of immune-mediated diabetes

- "Stiff-man" syndrome
- Anti-insulin receptor antibodies
- Others

H. Other genetic syndromes sometimes associated with diabetes

- Down syndrome
- Klinefelter syndrome
- Turner syndrome
- Wolfram syndrome
- Friedreich ataxia
- Huntington chorea
- Laurence-Moon-Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Others

IV. Gestational diabetes mellitus

(ADA, 2013)

TYPE 1 DIABETES MELLITUS

Epidemiology of type 1DM:

Incidence and prevalence:

Type 1 diabetes mellitus (Type 1DM) is one of the most common endocrine and metabolic conditions in childhood. Data on incidence of childhood onset Type 1DM is very limited. Data from large epidemiological studies worldwide indicate that on an annual basis, the overall increase in the incidence of Type 1DM is around 3% and about 78 000 children under age 15 years develop Type 1DM worldwide ***(IDF, 2011).***

Two major international Type 1DM registries (DIAMOND and EURODIAB) were established in the 1980s. The primary goal of both projects was to establish a network for the prospective registration of newly diagnosed children with Type 1DM in geographically well-defined regions using a standard protocol ***(ISPAD, 2007).***

The worldwide geographic variation in the incidence of Type 1DM is striking. The overall standardized incidence varies from 0.1/100 000 per year in the Zunyi region within China to more than 40/100 000 per year in Finland in children under the age of 15 years. This almost 400-fold variation in incidence can hardly be explained by genetic factors alone, environmental

factors have long been implicated in the pathogenesis of Type 1DM both as initiators and potentiators of pancreatic β-cells destruction (***DIAMOND Project Group, 2006)***

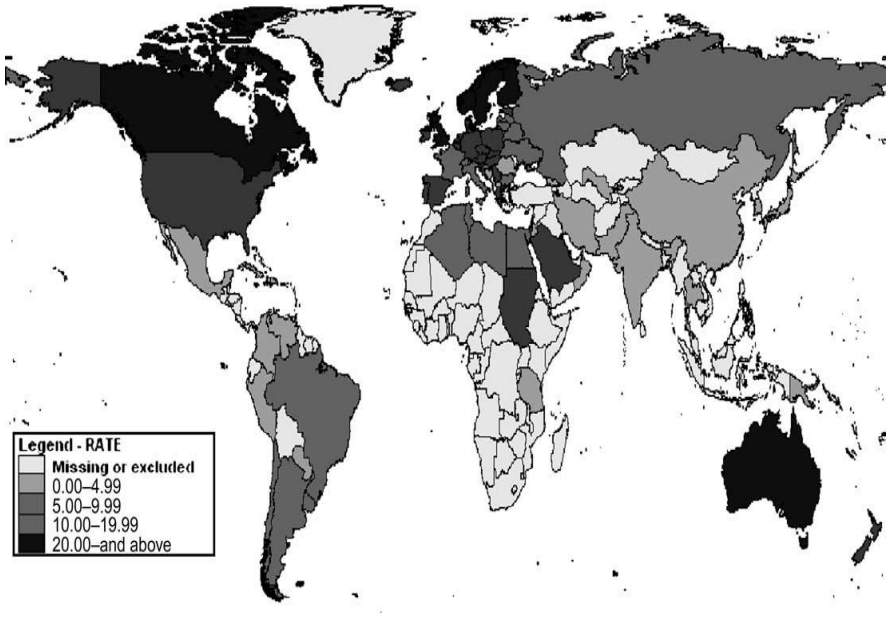

Figure (1): Map of published incidence rates (per 100 000) of type 1 diabetes in children ***(Solte´sz et al., 2006).***

The geographical variability in the incidence of Type 1DM may be explained by genetic variations. It is well-established that genetic factors, HLA system, influence the susceptibility to Type 1DM; however, the increases in Type 1DM incidence observed in many countries in recent years cannot be explained by genetic factors alone especially among ethnically similar populations, which highlights the role of the environment in disease evolution ***(Baker, 2006).***

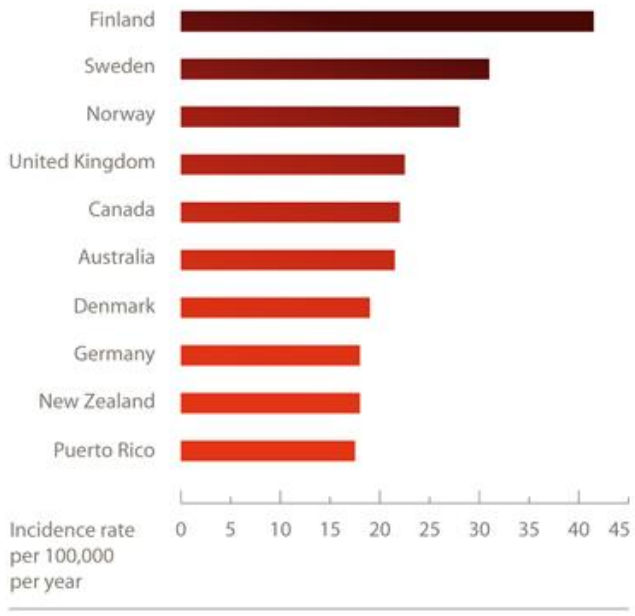

Figure (2): Top 10 countries: incidence rate for type 1 diabetes in children (0-14 years) ***(ISPAD, 2007).***

Among Eastern Mediterranean and Middle Eastern countries, the largest contribution to the total number of estimated childhood Type 1DM cases comes from Egypt which accounts for about a quarter of the region's total. The incidence varies between 1/100 000 per year (Pakistan) and 8/100 000 per year (Egypt) in children under the age of 15 years ***(Soltesz et al., 2006).***

Epidemiological incidence studies define the 'onset of type 1 diabetes' by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis ***(DIAMOND Project Group, 2006)***.

Egypt is located on the northeastern corner of Africa and has the largest settled population among the Arab countries. The Nile Delta is one of the most densely populated and cultivated regions in Egypt. Egypt is divided into 28 governorates, nine of them located in the Nile Delta such as; Dakahlia, Damietta, Kafr el-Sheikh and Gharbia; each is subdivided into urban and rural area. Type 1DM incidence and prevalence showed a progressive increase among children aged from 0 to 18 years living in the Nile Delta region ***(El-Ziny et al., 2014).***

Figure (3): Geographic map for the Nile Delta region, Area of the study; (Dakahlia, Damietta, Kafr El-Sheikh, Gharbia and other governorates) ***(El-Ziny et al., 2014).***

Higher Type 1DM occurrence was observed in rural areas and female predominance was evident. Seasonality in Type 1DM diagnosis was documented with a peak occurring in

winter. Our observations confirm the need to develop a national registry for Type 1DM and the need for further multicenter epidemiological research studies covering the whole country to define the nationwide Type 1DM incidence and the related health data in Egypt ***(El-Ziny et al., 2014)***.

Age-specific incidence:

In most registries, the age-specific incidence rates are calculated and presented using 5 year age groups (0–4, 5–9 and 10–14 year) separately for boys and girls. In general, the incidence increases with age, the incidence peak is at puberty with the associated gender effect ***(Soltesz et al., 2007).***

The incidence of childhood Type 1DM is not uniform at all ages. In most registries, the typical pattern of Type 1DM occurrence by age showed that the incidence increases with age and peaks generally in the peripubertal period with the associated gender effect which starts 1-2 years earlier in girls compared to boys. In children under age 15, DIAMOND Project Group reported a higher risk of developing Type 1DM in the 10-14 year age group, while the age group 5-9 years had a medium risk and the age group 0-4 years had a lowest risk. The age group 10-14 years had about twice the risk of developing Type 1DM compared to children younger than 5 years and this trend did not vary by gender. However, this is not a consistent observation since an increased incidence of childhood Type

1DM in the age group younger than 5 years compared to the older age groups has been reported in a multicenter study for childhood Type 1DM in Europe ***(Patterson et al., 2009).***

In general, the incidence increases with age, the incidence peak is at puberty. After the pubertal years, the incidence rate significantly drops in young women, relatively high in young adult males up to the age 29–35 years. Prospective national and large international registries (DIAMOND and EURODIAB) demonstrated an increasing trend in incidence in most regions of the world over the last few decades and increases seem to be the highest in the youngest age group ***(Soltesz et al., 2007).***

Aetiology of type 1DM:

A. Genetic susceptibility:

Type 1A diabetes mellitus results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. This process occurs in genetically susceptible subjects, is probably triggered by one or more environmental agents, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. Thus, genetic markers for type 1A diabetes are present from birth, immune markers are detectable after the onset of the autoimmune process, and metabolic markers can be detected with sensitive tests once enough ß-cell damage has occurred, but before the onset of symptomatic hyperglycemia. This long latent

period is a reflection of the large number of functioning beta cells that must be lost before hyperglycemia occurs. Type 1B diabetes mellitus refers to non-autoimmune pancreatic islets destruction (Type 1B diabetes) ***(Concannon et al., 2008).***

Susceptibility to autoimmune type 1diabetes is determined by multiple genes; in a recent metaanalysis more than 40 distinct genomic locations provided evidence for association with type 1 diabetes. HLA genes having the strongest known association, there is linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci ***(Barrett et al., 2009)***.

B. Autoimmunity:

Autoimmunity against pancreatic islets was described in 1965, but the presence of antibodies (AB) against islets (the islet-cell cytoplasm antibodies; ICA) was first demonstrated in 1974 ***(Eisenbarth et al., 2008).***

Several clinically useful serum *Autoantibodies* can be detected during the preclinical period of type 1 diabetes, including; islet-cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), antibodies to tyrosine phosphatase-like proteins such as insulinoma associated protein (IA-2, and IA-2 beta) and antibodies to the cation efflux zinc transporter of islet beta cells (ZnT8) ***(Wenzlau et al., 2010).***

1. *Islet cell autoantibodies (ICAs)*; Children with type 1 diabetes who do not have islet-cell or other autoantibodies at presentation have a similar degree of metabolic decompensation as do children who have these antibodies, although those with more of the different types of antibodies appear to have the most accelerated islet destruction and a higher requirement for exogenous insulin ***(Mziaut et al., 2006).***

2. *Insulin autoantibodies (IAA)*; the early appearance of *anti-insulin antibodies* suggests that insulin is an important autoantigen. Once insulin is administered subcutaneously, essentially all individuals develop insulin antibodies, and thus insulin autoantibody measurements after approximately two weeks of insulin injections cannot be used as a marker of immune mediated diabetes (type 1A) ***(Nakayama et al., 2005).***

3. *Glutamic acid decarboxylase antibodies (GADA);* another important autoantigen against which antibodies are detected is the enzyme glutamic acid decarboxylase (GAD), which is present in the islets as well as in the central nervous system and testes. Antibodies to GAD (a 65-kD protein) are found in about 70 percent of patients with type 1 diabetes at the time of diagnosis. The anti-glutamic acid decarboxylase is the most durable antibody, may still be positive after 15 years of the establishment of DM ***(Jaeckel et al., 2003).***