INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most chronic illness in childhood. Individuals with T1DM have an absolute deficiency of insulin secretion primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate. There are usually serological markers of an autoimmune pathologic process ***(ISPAD and IDF, 2011).***

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations. A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months ***(Barrett et al., 2009).***

Presentation of T1DM can vary from non-emergency presentations which include polydipsia, polyuria, weight loss and enuresis; to severe dehydration, shock and diabetic ketoacidosis ***(ISPAD and IDF, 2011).*** The frequency of DKA at clinical onset of diabetes varies widely by geographic region from approximately 15% to 75%, inversely corresponding to the regional incidence (i.e. level of awareness in the community) of type 1 diabetes. DKA at diagnosis is more common in children < 5 years of age and in those social or economic situations that do not permit ready access to medical care ***(Vanelli et al., 2007).***

When checking for diagnosis of T1DM or confirming a diagnosis of T1DM, it is useful to consider what other medical

conditions might be possible such as T2DM, MODY diabetes, Cushing's disease, Diabetes Insipidus, flu, viral infection, sinus infection, asthma, bladder infection, other causes of weight loss, impaired glucose tolerance, pancreatitis, hemochromatosis, fructosuria and xylulosuria ***(ISPAD and IDF, 2011).***

Diagnostic difficulties occur and lead to late diagnosis in very young children, and misdiagnosis such as urinary tract infection, asthma or pneumonia, gastroenteritis or acute abdomen ***(ISPAD and IDF, 2011).***

Therefore, awareness of general practitioners and pediatricians with the presentations of T1DM in children and it's prevalence is of utmost importance for early diagnosis and management of the disease. Lack of awareness increases the likelihood of having the patient into ketoacidosis, thus increasing the risk of mortality and the financial burden on hospitals and families.

AIM OF THE WORK

- To assess the awareness of doctors with the clinical presentation of type 1 diabetes mellitus(T1DM) in children and adolescents.
- To assess the possible misdiagnoses in presentation of T1DM in children and adolescents.
- To assess the time needed for children and adolescents from presentation till diagnosis of T1DM.
- To asses impact of delay in newly diagnosed patient in outcome of the disease.

TYPE 1 DIABETES IN CHILDREN AND ADOLESCENTS

Definition

The term diabetes mellitus describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both ***(WHO, 2006).***

Inadequate insulin secretion and/or diminished tissue responses to insulin in the complex pathways of hormone action result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and/or action may coexist in the same patient ***(ADA, Diabetes Care, 2014).***

Type 1 diabetes mellitus (T1DM) is the most chronic illness in childhood, individuals with T1DM have an absolute deficiency of insulin secretion primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate ***(ISPAD & IDF, 2014).***

There are usually serological markers of an autoimmune pathologic process**,** including islet cell antibodies (ICA), insulin auto antibodies (IAA), Glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT-8) ***(ISPAD and IDF, 2011).***

Etiologic Classification of Diabetes Mellitus

Table (1): Etiological classification of diabetes

I. **Type 1** β-Cell destruction, usually leading to absolute insulin deficiency	A. Immune mediated	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** 1.Chromosome 12, MODY3 2.Chromosome 7, MODY2 3.Chromosome 20, MODY1 4. Other rare forms of MODY including Chromosome 13, MODY4 Chromosome 17, MODY5 Chromosome 2, MODY6 Chromosome 2, MODY7 Chromosome 9, MODY8 Chromosome 7, MODY9 5. TNDM 6.PNDM 7. Mitochondrial DNA mutation 8. Others	**B**. **Genetic defects in insulin action** 1. Type A insulin resistance 2. Leprechaunism 3. Rabson–Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others	**C**. **Diseases of the exocrine pancreas** 1. Pancreatitis 2.Trauma/pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalculous pancreatopathy 7. Others
D. **Endocrinopathies** 1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4.Phaeochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others	**E**. **Drug- or chemical-induced** 1. Vacor 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormone 6. Diazoxide 7. β-Adrenergic 8. Thiazides 9. Dilantin 10. α-Interferon 11. Others	**F**. **Infections** 1. Congenital rubella 2. Cytomegalovirus 3. Enterovirus 4. Others
G. **Uncommon forms of immune-mediated diabetes** 1. 'Stiffman'syndrome 2. Anti-insulin receptor 3. Autoimmune polyendocrine syndrome (APS) types I and II 4. Others	**H**. **Other genetic syndromes sometimes associated with diabetes** 1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Fried Reich's ataxia 6. Huntington's chorea 7. Laurence–Moon–Biedl syndrome 8. Myotonic 9. Porphyria 10. Prader–Willi syndrome 11. Others	
IV. **Gestational diabetes mellitus (GDM).**		

(ISPAD & IDF, 2014)

Type 1 diabetes aetiology

Absolute deficiency of insulin secretion and are prone to ketoacidosis, most cases are primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate ***(ISPAD and IDF, 2011).***

Type 1 diabetes is believed to result from a complex interplay between genetic predisposition, the immune system, and environmental factors ***(Hober et al., 2010).***

Pathogenesis of type 1 diabetes

Type 1 diabetes is characterized by chronic immunemediated destruction of pancreatic β-cells, leading to partial, or in most cases, absolute insulin deficiency. The majority of cases (type 1A) result from autoimmune mediated pancreatic β-cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. The etiology is multifactorial, however, the specific roles for genetic susceptibility, environmental factors, the immune system, and β-cells in the pathogenic processes underlying type 1 diabetes remain unclear.

Diabetes-associated autoantibodies, which are serological markers of β-cell autoimmunity, include GAD, IA2, IAA, and ZnT8 ***(Watkins et al., 2014).***

The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged

<10 yr, while GAD and IA-2 are associated with older age and GAD with female gender ***(Howson et al., 2011).***

Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; with more than 60 risk loci identified by genome-wide association studies ***(Barrett et al., 2009).***

Human leukocyte antigen (HLA) genotype confers approximately 50% of risk ***(Noble et al., 1996).***

The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1* 14:01-DQA1*01:01-DQB*05:03, and DRB1*07:01- DQA1* 02:01-DQB1*03:03. For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes ***(Erlich et al., 2008).***

However, <10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease ***(Knip, 2011).*** Individuals at increased risk of developing type 1 diabetes can be identified by a combination of diabetes-associated auto-antibodies, genetic markers, intravenous glucose tolerance test (IVGTT) and/or OGTT ***(Aly et al., 2006).***

The environmental triggers (infective and/or chemical) which initiate pancreatic β-cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms ***(Ziegler et al., 2013).***

Enterovirus infection has been associated with development of both islet autoimmunity and type 1 diabetes in many populations ***(Yeung et al., 2011).***

And enteroviruses have been detected in the islets of individuals with diabetes ***(Richardson et al., 2009).***

When the clinical presentation is typical of type 1 diabetes but antibodies are absent, then the diabetes is classified as type 1B (idiopathic). In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of DKA at presentation ***(Usher-Smith et al., 2011).***

Prevalence of type 1 diabetes

In recent decades there has been a rapid rise in the incidence of childhood type 1 diabetes worldwide, especially in those under the age of 5 ***(Diamond, 2006).***

Egypt: Diabetes comparative prevalence WHO standard (2011): 16.60%-Incidence type 1 diabetes (0-14) per 8.00:100.000.

Eastern Mediterranean and the Middle East: Rates vary between 1/100,000 per year (Pakistan) and 8/100,000 per

year (Egypt). The IDF Atlas has however reported a rapid rise in Kuwait, with a recent incidence of 22/100,000 per year**.**

Global incidence rate of type 1 diabetes in children (0-14) years (cases per 100,000 population per year), in Egypt 8-12 per 100,000 ***(IDF Diabetes Atlas, 2012).***

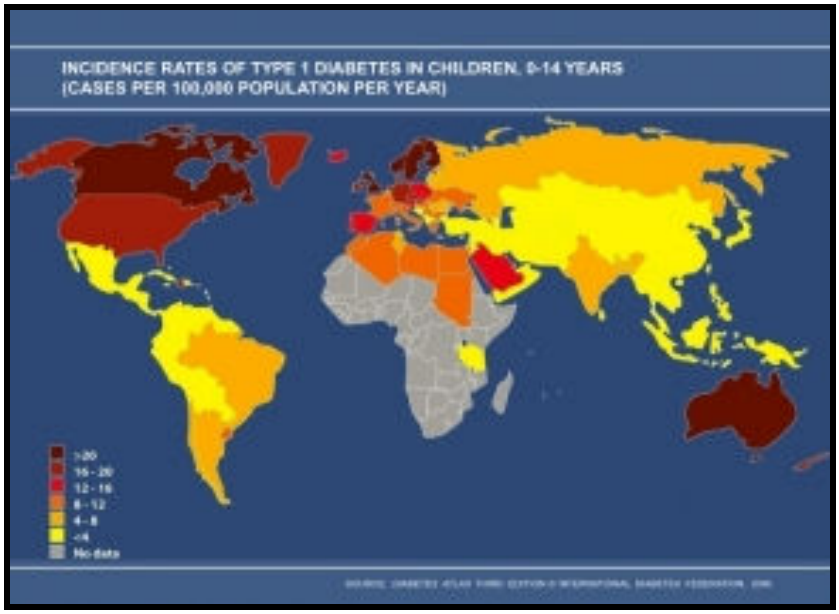

Figure (1): Global incidence of type 1 DM ***(IDF Diabetes Atlas, 2012).***

T1DM epidemiology study (1600 patients) in the Nile Delta region of Egypt, T1DM incidence and prevalence were found to show an increase over the past 18 years (1994-2011). Incidence and prevalence were higher in females (55.7%) and more cases were found to originate from rural areas (58.4%) ***(El-Ziny et al., 2012).***

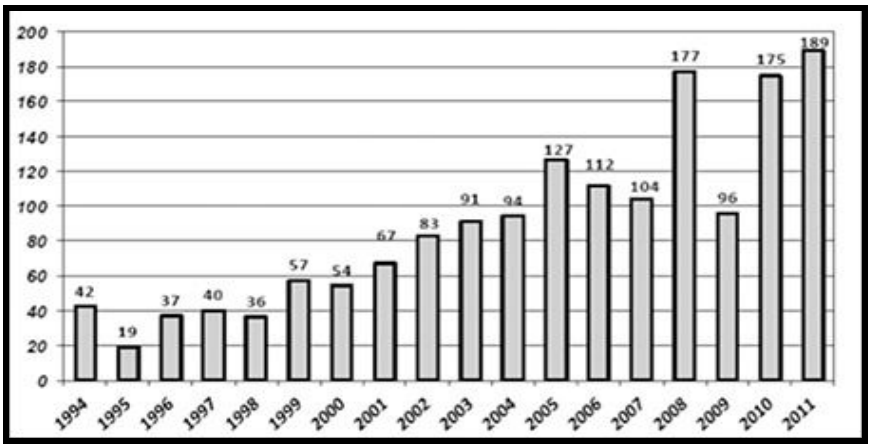

Figure (2): Annual numbers of new patients with type 1 diabetes mellitus (T1DM) among children aged 0-18 years in the Nile Delta region (1994-2011) ***(El-Ziny et al., 2012).***

Presentation of type 1 diabetes

1- Preclinical diabetes.

Preclinical diabetes refers to the months or years preceding the clinical presentation of type 1 diabetes when antibodies can be detected as markers of beta cell autoimmunity:

- Islet cell auto antibodies (ICA).
- Glutamic acid decarboxylase auto antibodies (65K GAD isoform).
- IA2 (also known as ICA 512 or tyrosine phosphatase) auto antibodies.
- Insulin auto antibodies (IAA).

2- Presentation of diabetes.

3- Partial remission or honeymoon phase.

4- Chronic phase of lifelong dependency on administered insulin ***(NIDDK, 2012).***

Table (2): Criteria for the diagnosis of diabetes mellitus

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 (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h. Or
III- Two hour post load glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT. • The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g or
IV- HbA1c >6.5%.

(ISPAD & IDF, 2014)

Table (3): Clinical characteristics of type 1, type 2 and monogenic diabetes in children and adolescents

Characteristic	Monogenic	Type 1	Type 2
Genetics	Monogenic	Polygenic	Polygenic
Age of onset	6 months to young adulthood	Usually pubertal(or later)	Often post pubertal except GCK and NDM
Clinical presentation	Most often acute	Rapid Variable	from slow, mild (often insidious) to severe
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in NDM, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually >90%	Most countries <10%	(Japan 60–80%) 1–4%
Parent with diabetes	2-4%	80%	90%

(ISPAD & IDF, 2014)

Causes of type 1 diabetes

Diabetes type 1 is induced by one or more of the following:

1- Genetics

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its onset. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between. The strongest gene, insulin dependent diabetes mellitus 1(IDDM1), is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increase the risk for decreased histocompatibility characteristic of type 1. The risk of a child developing type 1 diabetes is about 10% if the father has it, about 10% if a sibling has it, about 4% if the mother has type 1 diabetes and was aged 25 or younger when the child was born, and about 1% if the mother was over 25 years old when the child was born.

2- Environmental

Environmental factors can influence expression of type 1. For identical twins, when one twin had type 1 diabetes, the other twin only had it 30%–50% of the time. Despite having exactly the same genome, one twin had the disease, where the other did not; this suggests environmental factors, in addition to genetic factors, can influence disease prevalence, Other indications of environmental influence include the presence of a 10-fold difference in occurrence among Caucasians living in different areas of Europe, and a tendency to acquire the

incidence of the disease of the destination country for people who migrate ***(ADA, 2010)***.

- Virus

One theory proposes that type 1 diabetes is a virus-triggered autoimmune response in which the immune system attacks virus-infected cells along with the beta cells in the pancreas. The Coxsackie virus family or rubella is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the islets of Langerhans are destroyed, decreasing endogenous insulin production. This distinguishes type 1's origin from type 2. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

This vulnerability is not shared by everyone, for not everyone infected by the suspected virus develops type 1 diabetes. This has suggested presence of a genetic vulnerability and there is indeed an observed inherited tendency to develop type 1. It has been traced to particular HLA genotypes, though the connection between them and the triggering of an autoimmune reaction is still poorly understood.

- Diet

Some researchers believe the autoimmune response is influenced by antibodies against cow's milk proteins.

Vitamin D in doses of 2000 IU per day given during the first year of a child's life has been connected in one study in northern Finland (where intrinsic production of Vitamin D is

low due to low natural light levels) with an 80% reduction in the risk of getting type 1 diabetes later in life.

Having a short breastfeeding period as well as short attendance at day care are associated with an elevated risk of type 1 diabetes in Czech children ***(ADA, 2010)***.

- Chemicals and drugs

Some chemicals and drugs preferentially destroy pancreatic cells. Pyrinuron (Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental or intentional ingestion. Vacor was withdrawn from the U.S. market in 1979, but is still used in some countries. Zanosar is the trade name for streptozotocin, an antibiotic and antineoplastic agent used in chemotherapy for pancreatic cancer; it also kills beta cells, resulting in loss of insulin production. Other pancreatic problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin production ***(ADA, 2010).***

Symptoms of Diabetes

Symptoms of both type 1 and type 2 diabetes include:

- Frequent urination
- Excessive thirst
- Extreme hunger
- Sudden weight loss
- Extreme fatigue
- Irritability
- Blurred vision

In general, the symptoms of type 1 diabetes come on more abruptly and are more severe than those of type 2 diabetes ***(ADA, 2010).***

Presentation of type 1 diabetes

Table (4): Clinical characteristics at presentation of type 1 Diabetes

I-Non-emergency presentations	II-Emergency presentations (Diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemia)
1- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection 2- Vaginal candidiasis, especially in pre-pubertal girls 3- Chronic weight loss or failure to gain weight in a growing child 4- Irritability and decreasing school performance **5-** Recurrent skin infections	1- Moderate to severe dehydration 2- Frequent vomiting and in some cases, abdominal pain, which may be misdiagnosed as gastroenteritis 3- Continuing polyuria despite the presence of dehydration 4- Weight loss due to fluid loss and loss of muscle and fat 5- Flushed cheeks due to ketoacidosis 6- Acetone detected on the breath 7- Hyperventilation of diabetic ketoacidosis (Kussmaul respiration), characterized by an increased respiratory rate and large tidal volume of each breath, which gives it a sighing quality 8- Disordered sensorium (disoriented, semi-comatose, or rarely comatose) 9- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis) 10- Hypotension (a very late sign and rare in children with diabetic ketoacidosis)

(Wolfsdrof et al., 2009)