INTRODUCTION

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 ***(ISPAD, 2009).***

The differentiation between type 1, type 2 and monogenic diabetes has important implications for both therapeutic decisions and educational approaches. Regardless of the type of diabetes, however, the child who presents with severe fasting hyperglycemia, metabolic derangements and ketonaemia, will require insulin therapy initially to reverse the metabolic abnormalities ***(ISPAD, 2009).***

There are other types which includes genetic defects such as maturity onset diabetes of the young (MODY), pancreatic causes and endocrinopathies. MODY is a clinically and genetically heterogeneous group of disorders with autosomal dominant inheritance which account for 1-5% of all cases of diabetes mellitus in the industrialized countries ***(Nakhla & Polychronakoos, 2005).***

Diabetes complications are common and cost almost triple the annual cost of managing diabetes (***Bate and Jerums, 2003)***.

Complications are either short-term or long-term ones. Short-term complications include the occurrence of diabetic ketoacidosis or hypoglycemia. Long-term complications are either macro vascular or micro vascular (retinopathy, nephropathy or neuropathy) ***(Bate and Jerums, 2003).***

In the last decade, the use of electronic medical records (EMR) has been widely recommended as a method for reducing errors, improving the quality of health care, and reducing costs in ambulatory care settings***(Mokdad et al., 2001).***

EMRs have been shown to improve the quality of care for patients with chronic illnesses, such as diabetes. By facilitating the complex clinical information, EMRs could improve the coordination of tasks among members of health care team (***Burton et al., 2004***). Using electronic health records will lead to lower rates of missing clinical information and support evidence-based medicine (***Frijgling et al., 2002).***

AIM OF THE WORK

Evaluation of types of diabetes, types and regimens of different protocols, adequacy of diabetes control, frequency and severity of diabetic complications either acute or chronic among children and adolescents following up at the pediatric Diabetes Clinic, Ain Shams University Children's hospital.

TYPES and MANAGEMENT of DIABETES MELLITUS in PEDIATRICS

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. Ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly (***ISPAD, 2009).***

Table (1): Diagnostic criteria for diabetes in childhood and adolescence: *(ISPAD, 2009)*

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of Symptoms. Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the following three methods:
1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dl).
Casual is defined as any time of day without regard to time since last meal.
or
2. Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl).†
Fasting is defined as no caloric intake for at least 8 h.
or
3. 2-hour postload glucose ≥11.1 mmol/l (≥200 mg/dl) during an OGTT.

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG):

IGT and IFG are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes ***(Dahlquist, 2004).***

Categories of fasting plasma glucose are defined as follows:

• FPG<5.6 mmol/l (100 mg/dl) = normal fasting glucose

• FPG 5.6–6.9 mmol/l (100–125 mg/dl) = IFG

• FPG≥7.0 mmol/l (126 mg/dl) = provisional diagnosis of diabetes (the diagnosis must be confirmed) ***(ISPAD, 2009).***

The corresponding categories when the OGTT is used are as follows:

• 2 hour post load glucose <7.8 mmol/l (140 mg/dl) = normal glucose tolerance

• 2 hour post load glucose 7.8—11.1 mmol/l (140–199 mg/dl) = IGT

• 2 hour post load glucose>11.1 mmol/l (200 mg/dl) =provisional diagnosis of diabetes

(ISPAD, 2009)

Classification:

Table (2): Classification of types of DM:

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, HNF–1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF–4α (MODY1)
4. Chromosome 13, insulin promoter factor- (IPF-1; MODY4)
5. Chromosome 17, HNF–1β (MODY5)
6. Chromosome 2, *NeuroD1* (MODY6)
7. Mitochondrial DNA mutation
8. Chromosome 7, KCNJ11 (Kir6.2)
9. 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. Haemochromatosis
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 agonists
8. Thiazides
9. Dilantin
10. α -Interferon
11. Others

F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others

G. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others
4. Polyendocrine autoimmune deficiencies APS I and II

H. Other genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others

IV. Gestational diabetes

(Craig et al., 2009)

TYPE1 DIABETES MELLITUS

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at risk populations ***(Thunander et al., 2008)***.

Subtypes:

In type 1a there is evidence suggesting an autoimmune origin of β-cell destruction, mostly due to predominately activated auto reactive T cells that destroy beta cells which results in a progressive and predictable loss in insulin secretion function***. (Ize-Ludlow and Sperling, 2005).***

Type 1b form of diabetes is characterized by low insulin and C peptide levels similar to those in type 1a, although there is no evidence of an autoimmune etiology of the β-cell destruction. They are prone to ketoacidosis and depend on insulin to prevent metabolic deterioration. This idiopathic diabetes reflects the still limited knowledge of the etiology of many forms of diabetes (***Ize-Ludlow and Sperling, 2005).***

Etiological factors for type 1diabetes mellitus (T1DM):

The most often cited model of the natural history of T1DM suggests that genetically susceptible individuals with a fixed number of beta cells are exposed to a putative environmental trigger that induces beta cell autoimmunity. The degree of beta cell destruction required for symptomatic onset is also questioned, with recent studies suggesting that 40% to 50% of beta cells are viable at the onset of hyperglycemia ***(Haller et al., 2005).***

1-Auto immunity

Autoimmunity in T1DM typically has been identified by the presence of circulating antibodies to islet cell antigens, which in addition to their presence at the time of diagnosis often can be detected long before the disease becomes clinically evident. The development of islet reactive autoantibodies is a marker of ongoing autoimmune disease, but it is predominantly activated auto reactive T cells that destroy beta cells, which results in a progressive and predicable loss in insulin secretory function. Islet cell autoantibodies (ICAs), autoantibodies to glutamic acid decarboxylase (GAD65A), insulin autoantibodies (IAAs), and autoantibodies directed at a trans membrane tyrosine phosphate (ICA512A) are the most prevalent and best characterized but the potential for other autoantibody/auto antigen combinations remains, insulin autoantibodies (IA-2) has an extracellular, trans membrane, and cytoplasmic domain, and

autoantibodies to several forms of IA-2 have been observed in persons who have type 1 diabetes mellitus ***(Haller et al., 2005).***

IAAs are the first antibodies to appear but it should be measured in the first week of the start of exogenous insulin therapy, because antibodies to exogenously injected insulin also are detected and are indistinguishable from IAAs. GAD65A, like ICAs, are observed in 60% to 70% of new cases, unlike ICA, GAD65A often persist for many years after diagnosis ***(Haller et al., 2005).*** It is critical to note that autoantibodies have no known etiologic role in diabetes and -simply put- are believed to represent the "smoke of the fire" in the pancreas and not the fire itself. Recent studies in animal models of T1DM purposing a crucial role for B lymphocytes in disease development ***(Haller et al., 2005).***

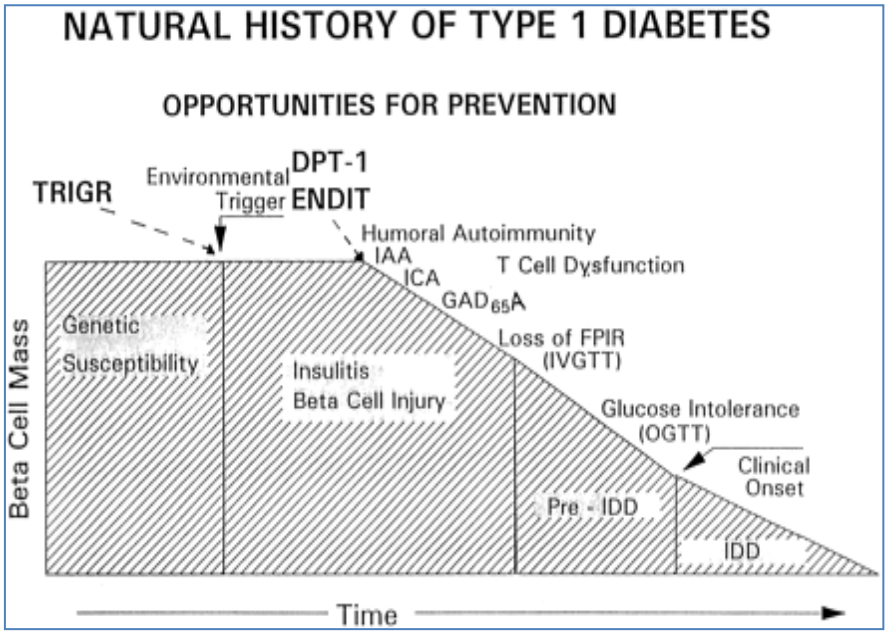

Fig. (1): The natural history of Type 1 diabetes ***(Haller et al., 2005).***

2-Genetic issues

There is no clear pattern of inheritance of childhood diabetes although there is familial aggregation due to the association of type 1 diabetes with certain genetic markers. In the higher incidence countries the risks to relatives of developing the disease when a member of the family has type 1diabetes, are as follows ***(ISPAD, consensus guidelines, 2007):***

- The risk of diabetes to an identical twin of a patient with T1DM is about (36%);
- For a sibling, the risk is approximately 4% by the age of 20 years and 9.6% by the age of 60 years compared with 0.5% for the general population.

T1DM is two to three times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%) ***(ISPAD, 2007).***

3-Environmental factors

Environmental factors are important because even identical twins have only a 30-60% concordance for type1 diabetes, and because incidence rates vary in genetically similar populations under different living conditions. No single factor has been identified, but infections and diet are considered the two most likely environmental candidates ***(Lamb, 2011)***.

A-Infection

Viral infections may be the most important environmental factor in the development of type1 diabetes, probably by initiating or modifying an autoimmune process. Instances have been reported of a direct toxic effect of infection in congenital rubella although most of these patients who develop diabetes have HLA and immune markers characteristic of type 1 diabetes ***(ADA, 2007)***. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease ***(ADA, 2007).***

B-Dietary factors

Dietary factors are also relevant. Breastfed infants have a lower risk for type1 diabetes, and a direct relationship exists between per capita cow milk consumption and incidence of diabetes. Some cow's milk proteins have antigenic similarities to an islet cell antigen such as bovine serum albumin and casein (which is a major protein fraction of cow's milk) ***(Haller et al., 2005).***

C. Bacterial infection:

Streptozotocin and Babilomycin A1 are macrolide antibiotics produced by Streptomyces species. Babilomycin A1 can cause glucose intolerance, decrease pro-insulin and insulin release, and decreased pancreatic islet size ***(Myers et al 2007).***

Frequency of T1DM:

Incidence rate

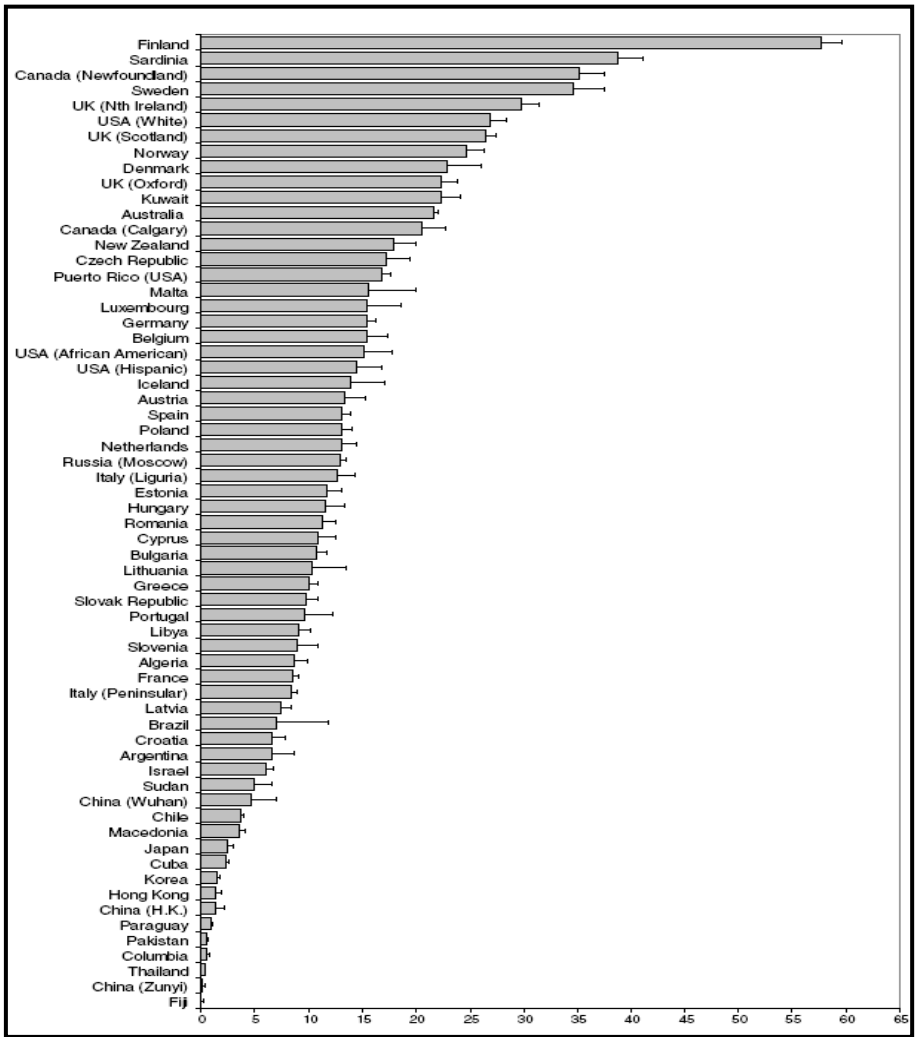

Fig. (2): Mean Annual Incidence Rates for Type 1 Diabetes (0–14 year age group) Comparing Different Countries in the World ***(*Craig *et al., 2009).***

Epidemiology of type 1 diabetes

In Egypt

The incidence of T1DM varies in different regions. Estimated the prevalence rate among school children (6-18) in Giza to be 0.33 per 1000 ***(Ghali and El Dayem, 1990)***.

Salem et al. (1998) reported that in the El Mansoura screening of 1000 school children (5-15) revealed that the prevalence of T1DM among them was 2 per 1000 and the point prevalence rate of TIDM in Heliopolis district in Cairo was 1.09/1000.

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years ***(Thunander et al., 2008).***

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 ***(Kawasaki et al., 2006).***

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations. Mean annual incidence rates for childhood type 1 diabetes (0–14 years age group) comparing different countries of the world are shown in Figure 1 (0.1 to 57.6 per 100,000) ***(Kawasaki et al., 2006).***

In Europe incidence rates show a close correlation with the frequency of HLA susceptibility genes in the general population ***(Urakami et al., 2008)***.

In Asia, the incidence of type 1 diabetes is extremely low: China 0.1 per 100 000 (3), Japan 2.4 per 100,000 And has a different and unique HLA association compared with Caucasians ***(Kawasaki, 2006).***

The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low risk HLA genotypes in some populations ***(Fourlanos et al., 2008).***

Gender differences in incidence are found in some, but not all, populations ***(Weets et al., 2004).***

A well-documented rise in the incidence has been noted in many countries, and in some reports there has been a disproportionately greater increase in those under the age of 5 years ***(Patterson et al., 2009).***

Phases of type 1 diabetes mellitus:

T1DM is characterized by having the following phases:

Preclinical DM:

Preclinical diabetes refers to the months or years preceding the clinical presentation of T1DM mellitus when antibodies can be detected as markers of beta-cell autoimmunity: Islet cell auto-antibodies, GAD65K, ICA512, IAAs refers to the months or years preceding the clinical presentation of T1DM mellitus when

antibodies can be detected as markers of beta-cell autoimmunity: Islet cell auto-antibodies, GAD65K, ICA512, IAAs.

In addition to these immunological and genetic markers [human leukocyte antigen (HLA) genotype and INS genotype], the risk of type1 diabetes mellitus can be further refined by measurement of insulin release in response to an intravenous glucose load [intravenous glucose tolerance test (IVGTT)] Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10^{th} percentile for age and sex-matched controls) confers a 60% risk over the next 5 years, Two or more islet antibodies raised without impaired first phase insulin release confer a 25–50% risk over the next 5 years ***(Couper and Donaghue,2007)***.

B-Presentation of T1DM is most often acute andrapid:

Clinical presentation of diabetes can vary from non-emergency presentations (e.g., polydipsia, polyuria, weight loss, and enuresis) to severe dehydration, shock and DKA***(Couper and Donaghue, 2007)***.

Partial remission or honeymoon phase in T1DM diabetes mellitus

In approximately 80 percent of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment. A recent definition is when the patient requires less than 0.5 units of insulin per kg of body weight per