Introduction

Diabetes mellitus is a common chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. Type-I D.M is the most common form of D.M. in children and adolescents (90% of cases) and account for only 5-10% of all cases of D.M ***(ISPAD, 2007)***.

It's an autoimmune disorder characterized by T-cell mediated destruction and progressive loss of pancreatic β-cells leading to eventual insulin deficiency and hyperglycemia. This disorder has a strong genetic component, inherited mainly through HLA complex, but the factors that trigger onset of clinical disease remain largely unknown ***(American Diabetes Association, 2005).***

The risk of developing microvascular complications is related mainly to the duration of diabetes and degree of glycemic control achieved over time (i.e./ HbA_1C 7.0% or less). Genetic factors also may influence the risk of complications. These complications are mainly renal microvascular complication (microalbuminurea or diabetic nephropathy), retinopathy and neuropathy (peripheral or autonomic) ***(Denerman, 2005).***

Few recent reports demonstrated elevated level of von Willebrand factor (VWF) in patients with type 1 DM; it's well known that VWF is degraded by a metallo protease, ADAMTS-13. It's hypothesized that elevated VWF level was due to reduced level of ADAMTS-13 ***(Mika, 2009).***

The deficiency of the VWF cleaving protease ADAMTS-13 causes platelet thrombosis in the microcirculation so it is hypothesized to have a role in the pathogenesis of diabetic microvasculer complications ***(Taniguchis et al., 2010)***.

Carotid intima media thickness (IMT) is a measurement of the thickness of arterial walls. It's increasingly used in clinical practice ***(Lorenz et al., 2010)***.

Carotid IMT is significantly higher in pediatric patients with type I DM. Few recent studies have addressed this issue ***(Rodriguez et al., 2010).***

Aim of the Work

Is to investigate the correlation between serum level of ADAMTS-13 and carotid intima-media thickness with the prevalence of micro- and macro-vascular complications in patients with type-1 diabetes mellitus. Also to correlate it with the markers of metabolic control.

CHAPTER (1): TYPE 1 DM IN CHILDREN

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels ***(ADA, 2013)***.

Classification:

WHO classified D.M. into clinical (normoglycemia, IGT/IFG, diabetes), and etiological types ***(ADA, 2013)*** as shown in table (1)**.**

Table (1): Etiological classification of diabetes mellitus ***(ADA, 2013)***

I. Type 1 diabetes (ß-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 ß-cell function:
B. Genetic defects in insulin action:
C. Diseases of the exocrine pancreas:
D. Endocrinopathies:
E. Drug- or chemical-induced:
F. Infections:
G. Uncommon forms of immune-mediated diabetes:
H. Other genetic syndromes sometimes associated with diabetes:
IV. Gestational diabetes mellitus (GDM)

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM), 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. T1DM remains the most common form of diabetes in childhood, accounting for approximately two-thirds of new diagnoses of diabetes in children ***(Duncan, 2006)***.

Type 1 DM is a disease with both acute and chronic complications that are associated with serious illness and shortened life. It has been estimated that average life span of individuals with diabetes is about 10 years shorter than nondiabetic general population ***(Alemzadeh and Wyatt, 2004)***. The aim of management is control of hyperglycemia, general health maintenance, psychological and emotional satisfaction, and prevention of acute and chronic complications ***(Devendra et al., 2004).***

The aspects of management include insulin therapy, nutritional management, exercise, educational aspects, and psychological aspects. A diabetes control and complications trial showed the importance of strict metabolic control in delaying and preventing complications ***(Ismail et al., 2008).***

Type 1 diabetes accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes or juvenile-onset diabetes ***(American Diabetes Association Committee, 2007).*** Type 1 is further classified to the following subtypes:

1. Type Ia (The autoimmune form):

This form of diabetes, which accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of pancreatic ß-cells representing about 90% of type 1 cases in Europe. The presence of other autoimmune disorders is highly raised ***(ADA, 2012).***

2. Type Ib (The idiopathic form):

Smaller group of type 1 diabetic patients exhibit no evidence of autoimmunity and the cause of insulin deficiency remains undefined.This cases are categorized as type 1b diabetes or idiopathic type 1 DM and are relatively more common in African and Asian population.This category is heterogenous, and remain poorly understood at this time ***(Ali, 2010).***

3. Type I c:

Another 1B subtype is the fulminant type 1 diabetes mellitus (FT1DM), which was first reported by ***Imagawa et al. in 2000***, is thought to be a unique subtype of type 1B diabetes. The initial reports of FT1DM were exclusively in Japanese population and accounted for about 20% of their T1DM ***(Imagawa et al., 2000).***

Outside Japan, ***Cho et al., (2007)*** reported prevalence for FT1DM of 7.1% in the newly diagnosed Korean T1DM patients. However, epidemiological study of FT1DM is

lacking in other Asian populations and its incidence and pathogenesis remain to be elucidated. While a search for FT1DM was reported to be negative in the Caucasian population, case reports on FT1DM had surfaced in different ethnic groups, predominantly from Asian origins ***(Jung et al., 2004; Taniyama et al., 2004; Moreau et al., 2008)***. However, the causative mechanism of FT1DM is currently unknown ***(Arai et al., 2011).***

Table (2): The clinical and biological characteristic of different subtypes of type 1 diabetes ***(Imagawa et al., 2000)***

	Type 1a	Type 1b	Type 1c
Signs of anti-islet autoimmunity	+	-	-
Duration of symptoms Before diagnosis	8 months	7 months	< 1 week
Ketosis, ketoacidosis at diagnosis	frequent	frequent	Constant
Blood glucose levels at diagnosis	↑↑	↑↑	↑↑↑
HbA_Ic at diagnosis	↑↑	↑↑	Normal or slightly elevated

Epidemiology

The incidence of childhood type 1 diabetes (T1DM) varies based upon geography, age, gender, family history, and ethnicity.

Geographical variation

The incidence of childhood T1DM varies worldwide ***(Silink, 2002)***. In Europe and China, the risk appears to rise as the geographical latitude (distance from the equator) increases ***(Waldhör et al., 2000)***. This North-South variation is not found in the United States, even after adjusting for racial and ethnic variation ***(Liese et al., 2010)***.

When people relocate from a region of low to high incidence, their risk of developing T1DM also increases, suggesting a causative role for environmental factor(s). However, wide variations in incidence occur between neighboring areas of similar latitude, suggesting the presence of other contributing risk factors and demonstrating the complexity of the pathogenesis of T1DM ***(Ross, 2003)***.

The highest reported incidences of T1DM occur in Finland and Sardinia (37 to 45 per 100,000 children younger than the age of 15 years). Rates in these countries are almost 400 times that of Venezuela and parts of China, which have the lowest incidence (0.1 to 0.5 per 100,000 children) ***(Plotnick et al., 2005).***

Diabetes prevalence in some Eastern Mediterranean countries is among the highest in the world. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar where the incidence of type 1 diabetes is reported to be 8–10 per 100 000 population per year in children aged <15 years ***(WHO, 2006)***.

Age and gender

The age of presentation of childhood onset T1DM has a bimodal distribution, with one peak at four to six years of age and a second in early puberty (10 to 14 years of age) (fig.1) ***(Felner et al., 2005)***. Overall, about 45 percent of children present before 10 years of age ***(Dabelea et al., (2007).***

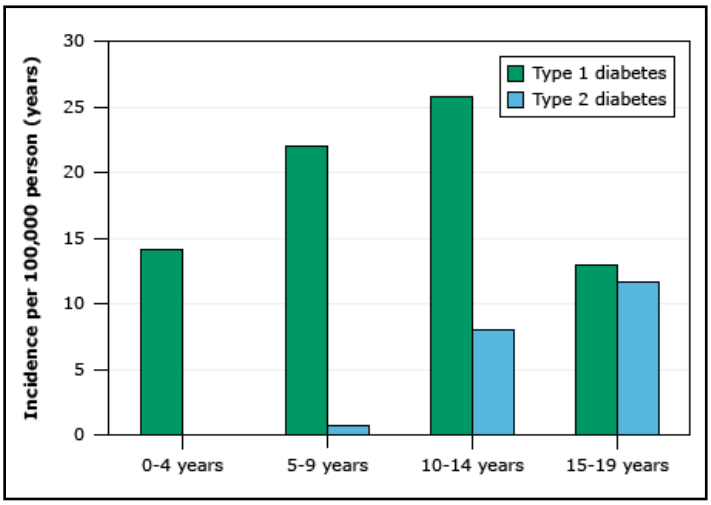

Fig. (1): Incidence of type 1 and type 2 diabetes mellitus in youth in the United States ***(Dabelea et al., (2007)***

Although most autoimmune diseases are more common in females, there appears to be no gender difference in the overall incidence of childhood T1DM ***(Dabelea et al., (2007)***. However, in select populations, T1DM occurs more frequently in males. As an example, older males of European origin (≥13 years of age) are more likely to develop T1DM than females of similar age and geographic location, with an approximate 3:2 male to female ratio ***(Harjutsalo et al., 2008).***

In Egypt, the prevalence rate of Type 1 DM among school children in Heliopolis district in Cairo was 1.09/1000 with male predominance ***(Salem et al., 1990)*** and in El Manyal district, the prevalence was 1.12/1000 school children with female predominance ***(Ghali and El-Dayem, 1990).***

Pathogenesis and Risk factors

Both genetic and environmental factors contribute to the risk of developing type 1 diabetes mellitus (T1DM) (fig. 2) ***(Gillespie, 2006)***.

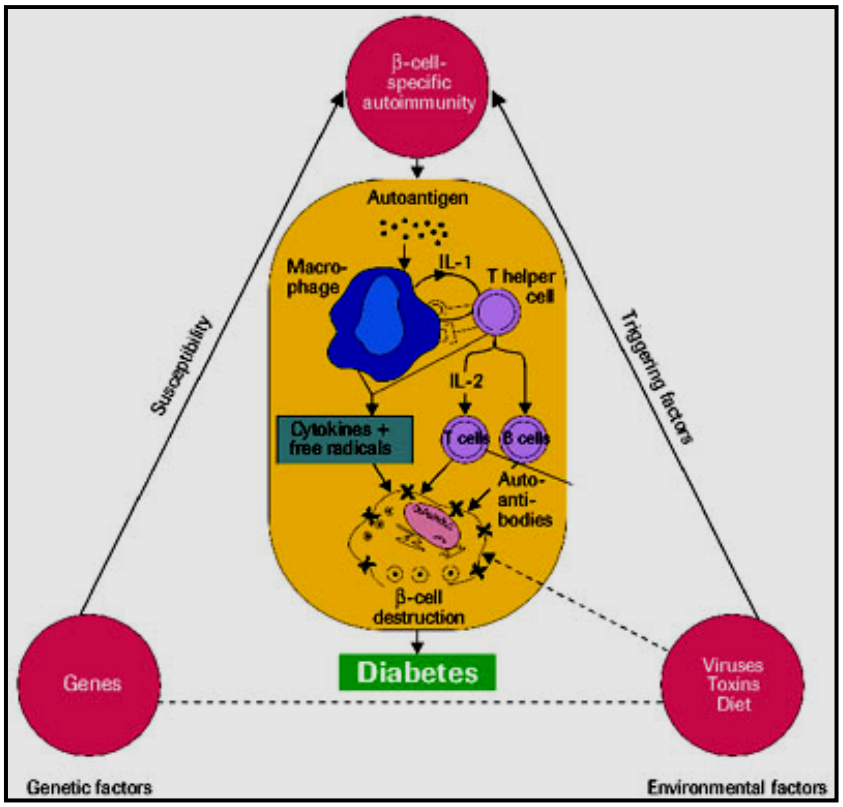

Fig. (2): Pathogenesis of type 1 diabetes ***(Gillespie, 2006).***

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 ***(Alves et al., 2012)***.

This long latent period is a reflection of the large number of functioning beta cells that must be lost before hyperglycemia occurs (fig.3). Type 1B diabetes mellitus refers to non-autoimmune islet destruction (Type 1B diabetes) ***(Cooper et al., 2008)***.

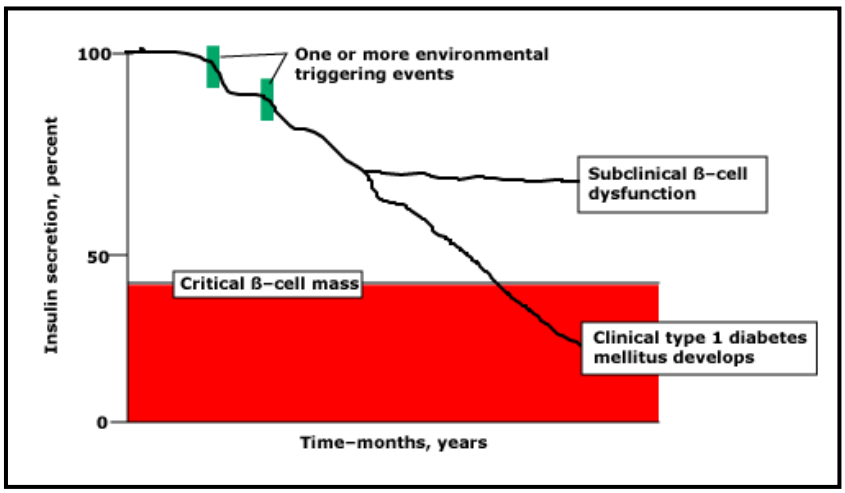

Fig. (3): Time course of the development of type 1 diabetes ***(Cooper et al., 2008)***

Genetic susceptibility

The lifetime risk of developing T1DM is significantly increased in close relatives of a patient with T1DM ***(Steck et al., 2005)***

- No family history – 0.4 percent
- Offspring of an affected mother – 1 to 4 percent
- Offspring of an affected father – 3 to 8 percent
- Offspring with both parents affected – reported as high as 30 percent ***(Guo and Tuomilehto, 2002)***
- Non-twin sibling of affected patient – 3 to 6 percent
- Dizygotic twin – 8 percent
- Monozygotic twin – 30 percent within 10 years of diagnosis of the first twin, and 65 percent concordance by age 60 years ***(Redondo et al., 2008)***

These observations of familial and ethnic risk factors are most likely the consequences of gene polymorphisms in the major histocompatibility complex (MHC) or other genetic susceptibility regions. Details regarding genetic susceptibility and the genes that increase the risk of T1DM are presented elsewhere ***(Guo and Tuomilehto, 2002).***

Polymorphisms of multiple genes are reported to influence the risk of type 1A diabetes (including, HLA-DQalpha, HLA-DQbeta, HLA-DR, preproinsulin, the PTPN22 gene, CTLA-4, interferon-induced helicase, IL2 receptor (CD25), a lectin-like gene (KIA0035), ERBB3e,

and undefined gene at 12q) ***(Smyth et al., 2006)***. A meta-analysis of data from genome-wide association studies confirmed the above associations and identified four additional risk loci (BACH2, PRKCQ, CTSH, C1QTNF6) associated with an increased risk of type 1 diabetes ***(Cooper et al., 2008).***

In addition, some loci conferring shared risk for celiac disease (RGS1, IL18RAP, CCR5, TAGAP, SH2B3, PTPN2) have been identified. Most loci have small effects, and the variants studied are common. The CCR5 association is of interest in that a 32-base pair insertion deletion in a chemokine receptor, CCR5, results in a loss of function and, when homozygous, a twofold decrease in risk of type 1 diabetes ***(Smyth et al., 2008)***.

MHC genes

The major susceptibility genes for type 1 diabetes (called IDDM1 for the MHC locus) are in the HLA region on chromosome 6p. This region contains genes that code for MHC class II molecules expressed on the cell surface of antigen-presenting cells such as macrophages. These MHC molecules consist of alpha and beta chains that form a peptide-binding groove in which antigens involved in the pathogenesis of type 1 diabetes are bound. MHC binding of antigen allows it to be presented to antigen receptors on T cells, which are the main effect or cells of the destructive autoimmune process ***(Pugliese, 2004)***.

The ability of these class II molecules to present antigens is dependent in part upon the amino-acid composition of their alpha and beta chains. Substitutions at one or two critical positions can markedly increase or decrease binding of relevant autoantigens and therefore the susceptibility to type 1 diabetes ***(Ettinger et al., 2000)***.

In particular, more than 90 percent of patients with type 1 diabetes carry either HLA-DR3, DQB1*0201 (also referred to as DR3-DQ2) or -DR4, DQB1*0302 (also referred to as DR4-DQ8), versus 40 percent of controls with either haplotype; furthermore, about 30 percent of patients have both haplotypes (DR3/4 heterozygotes), which confers the greatest susceptibility ***(Pugliese, 2004)***.

Non-MHC genes

Although important, the MHC susceptibility genes are not sufficient to induce type 1 diabetes, suggesting polygenic inheritance in most cases. An important component of the susceptibility to type 1 diabetes resides in certain non-MHC genes that have an effect only in the presence of the appropriate MHC alleles ***(Barker et al., 2004)***.

In particular, polymorphisms of a promoter of the insulin gene and an amino acid change of a lymphocyte-specific tyrosine phosphatase (termed lyp, PTPN22) are associated with the risk of type 1 diabetes in multiple populations. A repeat sequence in the 5' region of the insulin gene is associated with greater insulin expression in

the thymus and it is hypothesized that this contributes to decreasing the development of diabetes ***(Pugliese, 2004)***. The polymorphism of the protein tyrosine phosphatase (PTP) gene influences T cell receptor signaling, and the same polymorphism is a major risk factor for multiple autoimmune disorders ***(Kyogoku et al., 2004)***.

A polymorphism in the cytotoxic T-lymphocyte-associated antigen-4 gene was shown to be associated with the risk of type 1 diabetes in a meta-analysis of 33 studies involving over 5000 patients ***(Kavvoura and Ioannidis, 2005).***

Autoimmunity

Islet cell autoantibodies (ICAs) were first detected in serum from patients with autoimmune polyendocrine deficiency; they have subsequently been identified in 85 percent of patients with newly diagnosed type 1 diabetes and in prediabetic subjects. Radio assays are available to detect autoantibodies which react with specific islet autoantigens ***(Ettinger et al., 2000)***.

Children with type 1 diabetes who do not have islet-cell or other autoantibodies at presentation have a similar degree of metabolic de-compensation 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 during the second year of clinical disease ***(Imagawa et al., 2001)***.