Introduction

Diabetes Mellitus is the commonest endocrine metabolic disorder of childhood ***(Salem et al., 1990).***

Childhood type 1 diabetes results from immune – mediated destruction of pancreatic insulin – producing cells ***(Atkinson and Maclaren, 1994)***. The immune response leading to this destruction is thought to be of the T-helper (Th1) type ***(Solimena and DeCamille, 1996)***, whereas the type of immune response in asthma and atopy is though to be of Th2 type ***(Del Prete, 1992)***. This has raised questions as to whether decreased risk of asthma and atopy among children with type 1 diabetes is due to reciprocal effect of Th 1 and Th 2 immune responses ***(Douek et al., 1999; Dahlqvist et al., 2000).***

There is evidence that CD4 (+) CD 25 (high) T-regulatory cells are important, for establishing tolerance to allergens, but information in children is limited ***(Jartti et al., 2007).***

Type 1 diabetes is a T-cell–mediated disease that is associated with loss of immunological tolerance to self-antigens. The mechanisms involved in maintenance of peripheral tolerance include a specialized subset of regulatory T-cells (Treg) within the $CD4^{+}CD25^{+}$ T-cell population, but the function and phenotype of these cells in type 1 diabetes have not been investigated ***(Lindley et al., 2005).***

Aim of the Work

The aim of work was:

a) To assess the frequency of asthma and atopy among individuals with type 1 diabetes in childhood and adolescence and among sex and age- matched unaffected population control subjects.

b) To establish whether genetic and/or environmental factors predisposing to asthma and atopy contribute to the association between asthma and diabetes.

c) To assess role of peripheral blood CD4+ CD25+ T-cells in diabetes and atopy.

Diabetes Mellitus

Definition:

Diabetes mellitus 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 differentorgans, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association [ADA], 2010).***

Classification of diabetes mellitus:

Finally, there are a variety of uncommon and diverse types of diabetes, which are caused by infections, drugs, endocrinopathies, pancreatic destruction and genetic defects.These unrelated forms of diabetes are classified separately ***(American Diabetes Association, 2010) and Expert Committee, 2000).***

Table (1): Etiological classification of diabetes mellitus ***(ADA, 2010).***

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:

1. Chromosome 12, HNF-1 (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4 (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1 (MODY5)
6. Chromosome 2, Neuro D1 (MODY6)
7. Mitochondrial DNA
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. Pheochromocytoma
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. 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

H. Other genetic syndromes sometimes associated with diabetes:

1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's 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

4- Gestational diabetes mellitus (GDM)

Type 1 Diabetes Mellitus (T1D)

Type 1 diabetes is the form of the disease caused by B-cell destruction. This condition is characterized by severe insulin deficiency and dependence on exogenous insulin to prevent ketosis and to preserve life, it was previously called insulin dependent DM. The natural history of this disease indicates that there is preketotic, non-insulin-dependent phase before the initial diagnosis (phase of prediabetes) ***(Ize-ludlow and sperling,2005).***

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 the β-cells of the pancreas. ***(ADA 2010).***

Frequency:

. In the US: Over all incidence is approximately 15 cases per 100,000 individuals annually and probably increasing. An estimated 3 children out of 1000 develop T1D by the age of 20 years ***(ADA,2007).***

. Internationally: DM exhibits wide geographic variation in incidence and prevalence. Annual incidence varies from 0.61 cases per 100,000 persons in china, to 41.4 cases per 100,000 in Finland. Substantial variations exist between nearby countries with different lifestyles, such as Estonia and Finland, and between genetically similar populations such as those in Iseland

and Norway. These variations strongly support the importance of environmental factors in the development of T1D. Most countries report that incidence rates have at least doubled or more in the last 20 years. Incidence appears to increase with distance from the equator ***(ADA, 2007).***

. In Egypt: The incidence of T1D varies in different regions. ***Ghaly and El Dayem, (1990),*** estimated the prevalence rate among school children (6-18) years in Giza to be 0.33 per 1000.

In El-Mansura: A screening survey of school children (5-15 years) revealed that the prevalence rate of type 1 diabetes was 2/1000 ***(Ali et al., 1986).***

Egypt is in the world top 10 in terms of highest number of people with diabetes in 2003 (3.4 million) and highest projected number of people with diabetes in 2025 (7.8 million) ***(www.idf.org, 2006).***

Race:

- Different environmental effects on T1D development complicate the influence of race, but racial differences clearly exist.
- Whites have the highest reported incidence of T1D; Chinese have the lowest.
- TID is 1.5 times more likely to develop in American whites than in American blacks or Hispanics.

- Current evidence suggests that when immigrants from an area with low incidence move to an area with higher incidence, their T1D rates tend to increase toward the higher level ***(ADA,2007).***

Sex:

- The influence of sex varies with the overall incidence rates.
- Males are at greater risk in regions of high incidence particularly older males, whose incidence rates often show seasonal variation.
- Females appear to be at a greater risk in low-incidence regions

(ADA, 2007).

Subtypes:

Type 1 is further classified to the following subtypes:

Type 1 a: (Autoimmune T1DM):

There is evidence suggesting an autoimmune origin of B-cell destruction, mostly determined by the presence of circulating antibodies against islet cells; insulin antibodies in the absence of exposure to exogenous insulin; or antibodies to glutamic acid decarboxylase, and/or islet cell associated phosphatase. This autoimmune entity is also associated with certain HLAs. Patients with type 1 a are also more likely to have other concomitant autoimmune disorders, such as autoimmune thyroiditis, Addison's disease, and celiac disease ***(Ize-Ludlow and Sperling, 2005).***

Type 1 b: (Idiopathic T1DM):

Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. 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 β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go ***(ADA 2010).***

Table (2): The clinical and biological characteristics of the different types of T1DM:

	Type 1 a	**Type 1 b**
Sign of anti-islet autoimmunity	+	–
Duration of symptoms before diagnosis	8 months	7 months
Ketosis, ketoacidosis at diagnosis	Frequent	Frequent
Blood glucose levels at diagnosis	↑↑	↑↑
HbA1c at diagnosis	↑↑	↑↑

(Ize-Ludlow andSperling, 2005).

Pathophysiology of type 1 diabetes:

When 90% of the functioning beta cells have been destroyed, the loss of insulin secretion becomes clinically significant. With the loss of insulin, (the major anabolic hormone), a catabolic state develops, which is characterized by decreased glucose utilization and increased glucose production via gluconeogensis and glycogenolysis, leading to hyperglycemia. In the state of insulin deficiency, levels of counter regulatory hormones (i. e. glucagon, epinephrine, growth hormone, and cortisol) are elevated. These hormones stimulate lipolysis, fatty acid release, and ketoacid production. When the blood glucose concentration is persistently above the renal threshold for glucose reabsorption (i.e. 180 mg/dl). The resultant glucosuria causes an osmotic diuresis with increased urine output and increased fluid intake. At the later stage of the disease. There is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide ***(American Diabetes Association, 2007).***

When the blood glucose is persistently above the renal threshold for glucose reabsorption (i.e. 180mg/dl),the resultant glucosuria causes an osmotic diuresis with increased urine output and increased fluid intake ***(Ratazan, 1996).***

Diabetes is generally regarded as a disorder of glucose metabolism because hyperglycemia is responsible for its major symptoms; however-insulin is a key regulator of lipid and protein metabolism as well as of carbohydrate metabolism.

Therefore, the relative or absolute insulin deficiency affects the whole of intermediate metabolism ***(Vendrame et al., 2004).***

Pathogenesis of T1D:

Type 1 DM is a multifactorial chronic disease in which there is selective destruction of ß-cells due to an autoimmune process, triggers as environmental factors, most often considered are viruses, diet, toxins and stress, in order of suspected involvement ***(Pickup and Williams, 2003).***

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined ***(ADA 2010).***

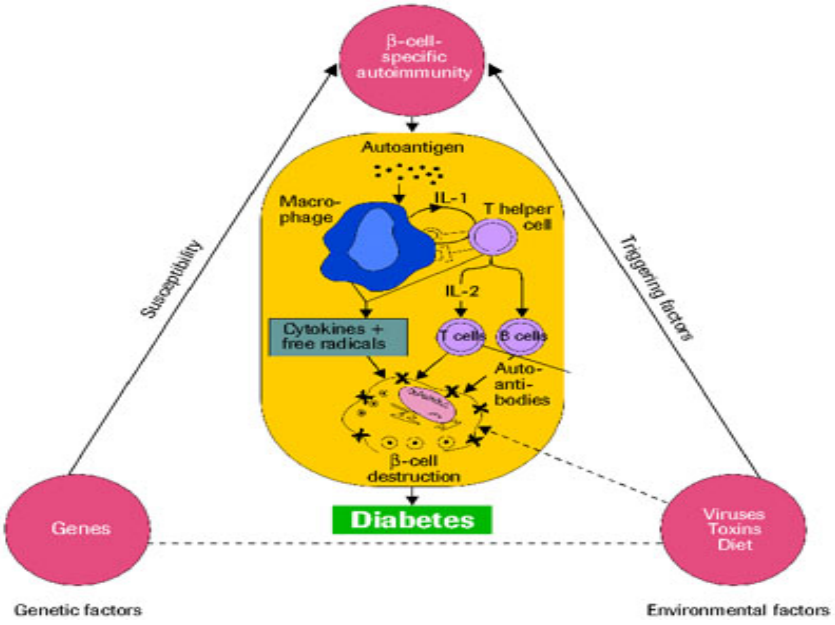

Fig. (1): Pathogenesis of T1DM ***(Kathleen, 2006).***

The development of T1DM has been divided into a series of stages:

- **Stage 1:** Genetic predisposition.
- **Stage 2:** Triggering of autoimmunity.
- **Stage 3:** Development of a series of auto-antibodies.
- **Stage 4:** Loss of B-cell function, as determined by intravenous glucose tolerance testing (metabolic defects).
- **Stage 5:** Overt DM
- **Stage 6:** Total or near total B-cell destruction with insulin dependence ***(Petrovsky and Schatz, 2003).***

1) Stage 1: Genetic Susceptibility

- T1DM is a ß-cell selective immune-mediated disease with a strong genetic background. Heritable susceptibility is conferred by at least 14 gene loci with the largest contribution from the human leukocyte antigen (HLA) region on chromosome 6 ***(Cerna et al., 2007).***

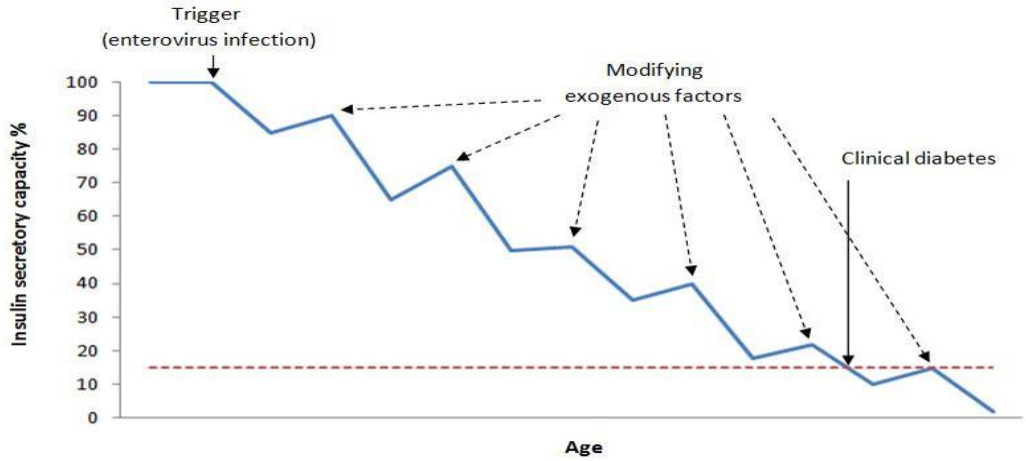

Fig. (2): Progression from genetic susceptibility to overt T1DM. According to this model, the disease process is triggered by an exogenous factor, driven by another environmental determinant, and modified by a series of environmental factors in individuals with increased genetic disease susceptibility ***(Knip, 2003).***

2) Stage II: Triggering of autoimmunity

Viral infections and dietary compounds are the most likely environmental factors contributing to the etiopathogenesis of T1DM**.** To resolve the controversy about the role of environmental factors in the pathogenesis of T1DM, The Environmental Determinants of Diabetes in the Youth **(TEDDY)**, a large international project, with the aim to evaluate the putative environmental triggers during the 15-year follow-up of several thousand newborn babies identified with HLA-DR, DQ genotypes associated with T1DM, has recently been initiated ***(Rewers and Zimmet, 2004).***

Viruses:

The seasonal variation in the emergence of the first signs of ß-cell autoimmunity suggests that infectious agents may play a role In the Induction of such autoimmunity. Viruses are thought to act as initiators, accelerators or precipitators of the disease, and may function by direct or indirect mechanisms ***(Vanderwerf et al., 2007).***

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease ***(ADA, 2010).***

Tenconi et al., (2007), reported that several viruses may be associated with T1DM in human such as Coxsackie A virus, echo virus, hepatitis virus, varicella virus, measles, polio and rota virus.

None of the routine childhood immunization has been shown to increase the risk of diabetes or pre-diabetic autoimmunity ***(Hviid et al., 2004).***

Nutritional:

1. Breast–feeding seems to provide protection against the risk of developing T1DM ***(Hummel et al., 2007).***
2. Early exposure to cow's milk was reported to be an environmental trigger of an immune response to insulin

during infancy. Molecular mimicry is involved as a possible mechanism in bovine serum albumin (BSA) mediated Islet cell autoimmunity. Many patients with new onset diabetes have IgG antibodies to BSA ***(Akerblom et al., 2005).***

3. As many as 5 - 10% of patients with T1DM have gluten-sensitive enteropathy (celiac disease) ***(Myśliwiec et al., 2008).***

4. Vitamin D has shown to have immunomodulatory specifically immunosuppressive characteristics. It may down regulate the autoimmune process that leads to overt diabetes ***(Mohr et al., 2008).***

El Samahy et ***al., (2001)*** studied the effect of T1DM and insulin deficiency on bone metabolism and bone mineral density. They performed DEXA scan on 40 T1DM children and adolescents with mean disease duration of 3 years. They documented osteopenia in 70% of the studied patients. They revealed that diabetes resulted in hypercalciurea with normal serum calcium, intestinal calcium malabsorption, and decrease in the concentration of 1,25 dihydroxy vitamin D.

Psychological stress:

Serious psychological stress or stressful life events as recent occurrence of traumatic events as parent death and accidents have been proposed as possible triggering factors for T1DM ***(Karavanaki et al., 2008a).***