Introduction

Diabetes mellitus is associated with metabolic and micro-vascular abnormalities as well as multi-organ and multi-system dysfunction. Pulmonary damage in diabetic patients arises from several mechanisms including biochemical changes in connective tissue especially in collagen and elastin. Non enzymatic protein glycosylation induced by chronic hyperglycemia has been proposed as one of the determinant mechanisms leading to diabetic micro-angiopathy Owing to its abundant connective tissue and diffuse micro-vascular circulation, the lung is thought to be a target organ for diabetic disease ***(Villa et al., 2004)***.

Another potential mechanism that may explain the findings of decreased lung function is decreased muscle strength in diabetic subjects because of defective muscle metabolism ***(Lazarus et al., 1997)***.

Diabetic lung involvement is best characterized as loss of physiological reserve. Restriction of vital capacity becomes physiologically significant when it impairs alveolar gas exchange ***(Hisia, 2002).***

Lung restriction in diabetes could result from chronic low grade tissue inflammation, micro-angiopathy, and/or of advanced glycation end products ***(Yeh et al., 2008)***.

Post mortem data has confirmed that diabetes does affect the pulmonary vasculature, with advanced glycoslation end product implicated in the thickening of the alveolar capillary membrane, in addition to changes within endothelial cells and type 2 pneumocytes. According to kaparianos and colleagues, assessment of the effect of diabetes on gas transfer (diffusing capacity (DLCO) using ventilation tests or scintigraghy gives conflicting results ***(Kaparianos et al., 2008)***.

Aim of the Work

To study the frequency of pulmonary function abnormalities “spirometric studies” in children and adolescent with type 1diabetes mellitus to correlate it with the parameters of metabolic control and to evaluate frequency of pulmonary micro-angiopathy in those patients.

Diabetes Mellitus

DEFINITION:

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defect in insulin secretion, action, or both ***(ADA, 2007)***.

DM is not a simple disease but it is a heterogeneous group of disorders in which there are distinct genetic pattern of inheritance as well as separate eitiolgic and physiologic mechanisms all leading to impairment of glucose metabolism ***(Gabir et al., 2000)***.

Systemic vascular dysfunction is a central part of the pathophysiology of both type I insulin dependent and type II non insulin dependent coronary heart disease is the leading cause of morbidity and mortality in diabeties and account for 60% of death in this group peripheral vascular disease, retinopathy and nephropathy are all more common in diabeties and lead to significant morbidity ***(Schallcwijlc et al., 2005)***.

The development and progression of diabetic complications are strongly releated to the degree of glycemic central ***(Ozmen and Boyuada, 2003)***.

Glucose is an inflammatory agent and has been demonstrated to increase reactive oxygen species (ROS) production when the endothelial cells are exposed to high levels of glucose in vitro ***(Lopez et al., 2008)***.

CLASSIFICATION:

Etiologic classification of diabetes mellitus

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

A. Immune-mediated
B. Idopathic

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 of diabetes

A- Genetic defects of B-cell function:
1- Chromosome 12,HNF-1 (MODY3)
2- Chromosome 7,glucokinase (MODY2)
3- Chromosome 20,HNF-4 (MODY1)
4- Chromosome 13,insulin promoter factor1(IPF; 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-Menenhall syndrome
4- Lipotrophic diabetes
5- Others

C- Diseases of the exocrine pancrease:
1- Pancreatitis
2- Neoplasia
3- Truma / pancreatectomy
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- Pentamide,
2- Nicotinic acid,
3- Glucocorticoids,
4- Thyroid hormone,

5- Diazoxide,
6- Thiazide
7- Dilantin
8- Adrenergic agonists
9- Intreferon
10- Other

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 syndrome,
4- Wolfram's syndrome
5- Laurence-Moon-Bledl syndrome
6- Porphyria.
7- Friedreich's ataxia
8- Prader-Willi syndrome
9- Huntington's chorea
10- Myotonic dystrophy
11- Others

IV- Gestational diabetes mellitus (GDM)

HNF = hepatocyte nuclear factor, **MODY** = maturity-onset diabetes of the young.

American diabetes Association (ADA, 2007)

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient ***(ADA, 2007).***

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories:

Type 1: diabetes.

Type 2: diabetes.

Table (1): Characteristic features of type 1 compared with type 2 diabetes in young people

Characteristics	Type 1	Type 2
Age	Throughout Childhood	Pubertal or later
Onset	Most often acute, rapid	Variable, from slow, mild to severe
Insulin dependence	Permanent, total, severe	Uncommon, but insulin required when oral hypoglycemic fail.
Insulin secretion	Absent or very low	Variable
Insulin sensitivity	Normal	Decreases
Genetic	Polygenic	Polygenic
Race/ethnics	All groups, but wide variability of incidence	Certain ethnics groups are at particular risk
Frequency	Usually 90%	Most countries 10%
Auto-immunity	Yes	No
Ketosis	Common	Rare
Obesity	No	Strong
Acanthosis nigricans	No	Yes

(Ramin and David, 2004)

<u>Type 1 is further to classified to the following subtypes:</u>

1- ***Type 1a (The auto-immune from):*** Auto-immune destruction of pancreatic B-cells representing about 90% of type 1 cases in Europe. The presence of other auto-immune disorders is highly raised ***(ADA, 2005)***.

2- ***The idiopathic form (type 1b):*** in which there is no evidence of auto-immunity, it represents about 10% of cases of type 1 DM in Europe ***(Salma, 2003)*.**

A publication from Japan has described what is thought to be another, new form of the disease where the onset was explosive with 4-5 days of sympotoms, HbA1c levels were still almost normal at diagnosis, there was a profound lack of insulin, extremely high blood glucose level and full ketoacidosis but there were no anti-islet auto-antibodies ***(Imagawa et al., 2000)***.

Table (2): The clinical and biological characteristics of the different subtypes of type 1 diabetes

	Type 1a	**Type 1b**	**Type 1c**
Signs of anti-islet auto-immunity	+	-	-
Duration of symptoms before diagnosis	8 months	7 months	< 1 week
Ketosis, ketoacidosis at diagnosis	Frequent	Frequent	Constant
Blood glucose levels at diagnosis	↑↑	↑↑	↑↑↑
HbA_{1c} at diagnosis	↑↑	↑↑	Normal or slightly elevated

(Imagawa et al., 2000)

EPIDEMIOLOGY

Diabetes mellitus is the most common endocrine-metabolic disorder of childhood and adolescence ***(Sperling, 2000).***

Diabetes is an epidemic in United States, affecting 8% of the population. The hallmark of diabetes is hyperglycemia due to either insulin deficiency insulin resistance ***(Lopez et al., 2008).***

In united states, even with increasing rate of type 2 diabetes, type I diabetes accounts for approximately 2/3 of new diagnosis of diabetes in patients < 19 years old age ***(Lipton et al., 2005)***.

INCIDENCE AND PREVALENCE:

The National diabetes statistics, (2007) stated that:

- About 186,300 people aged 20 years or younger have diabetes representing 0.2% of this age group.
- About one in every 400 children and adolescents have diabetes.
- Globally, there has been a dramatic increase in the prevalence of diabetes in recent years. It was estimated that in 2007, around 246 million people worldwide had diabetes and if current trends prevail, this figure is likely to jump to 380 million by the year 2025.
- Type 1 diabetes accounts for only 5-10% of those with diabetes.
- The overall risk for death among people with diabetes is about twice that of people without diabetes of a similar age group.
- Adults with diabetes have a risk of strokes and heart disease death rates about 2 to 4 times higher than non diabetics.
- Diabetic retinopathy causes 12000 to 24000 new cases of blindness each year.

- Diabetes is the leading cause of kidney failure accounting for 44% of new cases.
- Males and females have similar risk of type 1 DM with the pubertal peak of incidence in females preceding that in males by 1-2 years.
- There is bimodal peak of incidence, the first around 6 years of age and the other around 10 years of age.
- There is male excess in the incidence of type 1 diabetes particularly marked after the age of puberty.

In countries with higher incidence, the age of onset of DM indicates that:

- Diabetes under the age of 1 year is extremely uncommon.
- Incidence increases with age.
- There may be a minor peak at the age of 4-6 years.
- There is a major peak at the age of 10-14 years ***(ISPAD Guidelines, 2007).***

The incidence of type I DM in childhood shows a cyclic variation that is both seasonal and long term. Independent studies confirm that newly recognized cases occur with greater frequency in the autumn and winter month both in the northern and southern hemispheres ***(Ramin and David, 2004).***

Recent study of incidence and prevalence of T1DM in children and adolescents in four Egyptian Governorates (Fayoum, Minofeya, North Sainai and Sues) is held by ***Salem et***

al. (2007), showing a prevalence rate of 0.7/1000 and an incidence rate of 4.01/100.000.

PATHOPHYSIOLOGY:

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)***.

Glucose metabolism:

Uncontrolled type 1 DM leads to increase hepatic glucose output, reduced glucose uptake by peripheral tissues.

This combination leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is exceeded, glucosuria ensures. Glucose is an osmotic diuretic and an increase in renal loss of glucose is accompanied by loss of water, increase appetite and food intake (polyphagea) ***(Alemzadeh and Wyatt,2004).***

Lipid metabolism:

In uncontrolled type 1 DM there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. Mitochondrial oxidation of fatty acids generates acetyl COA which can be further metabolized into ketone bodies acetoacetate and hydroxybutyrate ***(Gylling et al., 2004)***.

These ketone bodies leave the liver and are used for energy production by the brain, heart and skeletal muscles. In type 1 DM, the increased availability of free fatty acids and ketone bodies exacerbate the reduced utilization of glucose furthering the increase in hyperglycemia. Production of ketone bodies in excess of the body ability to utilize them leads to ketoacideosis ***(Alemzadeh and Wyatt, 2004)***.

Protein metabolism:

Insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concentrations in plasma amino acids. These amino acids serve as precursors for hepatic and renal gluconeogensis ***(Alemzadeh and Wyatt, 2004)***.

Type I diabetes results from a cellular-mediated autoimmune destruction of B-cells of the pancreas. The rate of B-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others, mainly adults causing what is called latent auto-immune diabetes of adult (LADA) ***(Seissler, 2008).***

ETIOLOGY AND PATHOGENESIS OF TYPE I DIABETES:

Type 1 DM is a multi-factoriel chronic disease in which there is selective destruction of B-cells due to an auto-immune process, triggered as a result of environmental factors, most often considered are viruses, diet, toxins and stress, in order of suspected involvement ***(Pickup and Williams, 2003)***.

The development of type 1 DM has been divided into a series of stages. **Stage 1,** genetic predisposition; **stage 2**, triggering of auto-immunity; **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; and **stage 6**, total or near total B-cell destruction with insulin dependence ***(Petrovsky and Schatz, 2003)***.

1. Genetic factors.
2. Viruses.
3. Enviromental agents.
4. The immunology of type 1 diabetes.

1. Genetic factors:

Genetic predisposition probably accounts for about one third of susceptibility to type 1 diabetes ***(Bain et al., 2003)***.

Approximately 10% of cases of type 1 diabetes occur in families in which another first degree relative has type 1 diabetes, with the remainder of cases occurring spontaneously ***(Petrovsky and Schatz, 2003)***. Point estimates of risk or concordance in (MZ) monozygotic twin range from 30% to 70% ***(Fernandes et al., 2004)***. 6-8% for fathers, 2-4% for mothers and 6-12% if both parents have diabetes ***(Salma, 2003)***.

Approximately 50% of the genetic risk for type 1 diabetes is attributable to HLA region ***(Steck et al., 2005)***. The human leukocyte antigen (HLA) region is a cluster of genes

located within the major histocompatibility complex (MHC) on chromosome 6 ***(Donner et al., 2000)***.

HLA antigens are glyco-protein found on the surface of cells. They comprise classes I and II, which are encoded by different genes within the HLA region and this differ fundamentally in their structure ***(Abraham et al., 2001)***.

The HLA class II region DQBI and DRBI are of primary importance for disease susceptibility for type 1 diabetes have been observed with early onset of the disease. Moreover, neonates, infants and toddlers with type 1 diabetes than diabetic children diagnosed at a later age ***(Hathout et al., 2003)***.

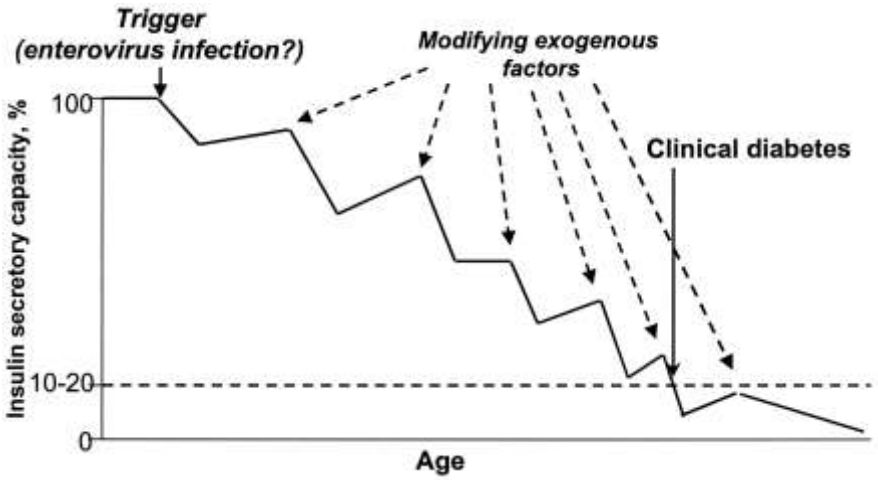

Fig. (1): Progression from genetic susceptibility to overt type I diabetes. According to this model, the disease process is triggered by an exogenous factor, driven by another environmental factors in individuals with increased genetic disease susceptibility ***(Knip et al., 2005).***

2. Viruses in the pathogenesis of type 1 diabetes:

An environmental trigger probably initiates auto-immunity. This results in an anti β cell immune responses leading to islet

infiltrates (insulitis), with the consequence of B cell injury, impairment of β cell function, and some loss of B cell mass ***(Yoon and Jun, 2003)***. As β cells are injured; a presumably secondary humoral immune response develops, with appearance of β cell auto-antibodies that characterizes this stage.

Seasonal variations in the diagnosis of type 1 diabetes have been considered as indirect evidence for infections exposure ***(Yoon and Jun 2004)***.

Infections caused by rubella, coxsaki B group and echoviruses might induce beta cell damage in genetically susceptible children if experienced during fetal life ***(Pundziute-Lycka et al., 2000).***

Enterovirus infection may precipitate the symptoms of clinical diabetes and play a role in the initiation of the beta-cell damaging process ***(Juhela et al., 2000)***.

3. Enviromental agents and type 1 diabetes:

Environmental factors:

Environmental agents might function as initiating factors for diabetes or might act as precipitating factors that convert preclinical diabetes into clinical disease in genetically susceptible individuals. This results in an β-cell function, and reduction of β-cell function, and reduction of β-cell mass ***(Yoon and Jan, 2004)***.