# INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. The absence, destruction, or other loss of ß-cells of the islets of Langerhans results in type ١ diabetes (T١DM) with a lifetime dependence on exogenous insulin ***(Porter et al., ٢٠٠٤).***

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 ***(American Diabetes Association (ADA), ٢٠١٣)***.

T١DM is the most common metabolic disease in childhood. Interplay between genetic susceptibility and environmental factors (triggering or suppressive) may account for the pathogenesis. The diabetes control and complications trial (DCCT) showed the importance of strict metabolic control in delaying and preventing complications ***(Ismail et al., ٢٠٠١).***

Diabetes in all its forms is one of the main cardiovascular risk factors. Two of ٣ diabetic patients will die as a result of cardiovascular complications, and approximately ٣٠٪ of patients treated in cardiovascular intensive care units have diabetes ***(Kengne et al., ٢٠٠٥).***

There was a significant association between diabetes and diastolic dysfunction leading to congestive heart failure in the absence of impaired systolic function ***(Kim et al., ٢٠٠١).***

However, controversies exist about the presence of cardiac abnormalities in young patients with type ١ DM ***(Elshahed et al., ٢٠٠٨).***

Plasma myeloperoxidase (MPO) is most abundantly expressed in neutrophil granulocytes (a subtype of white blood cells). It is a lysosomal protein stored in azurophilic granules of the neutrophil. MPO has a heme pigment, which causes its green color in secretions rich in neutrophils, such as pus and some forms of mucus ***(Klebanoff, ٢٠٠٥)***.

Plasma myeloperoxidaseis believed to be one of the most promising cardiac markers. It was demonstrated that an increased MPO level in patient's blood serves as a risk marker for atherosclerosis ***(Nambi, ٢٠٠٥)*** and coronary artery disease (CAD). It predicts the early risk of myocardial infarction, as well as the risk of other major adverse cardiac events in patients with chest pain ***(Baldus et al., ٢٠٠٣ and Brennan et al., ٢٠٠٣).*** Increased plasma MPO levels are associated with more advanced indices of systolic and diastolic dysfunction ***(Tang et al., ٢٠٠٦).***

MPO is believed to participate in the initiation and progression of cardiovascular diseases. It possesses potent pro-inflammatory properties and may contribute directly to tissue injury. Children with type (١) DM have substantially elevated plasma levels of myeloperoxidase ***(Heilman et al., ٢٠٠٩).***

The Tei index, obtained from tissue Doppler echocardiography (TDE-Tei index), has emerged as a new parameter that incorporates both systolic and diastolic time intervals to express global ventricular performance ***(Kargin et al., ٢٠١٠)***.

# AIM OF THE WORK

To estimate the level of plasma myeloperoxidase as a marker of oxidative stress in type ١ diabetic children & adolescents and to study its relation to myocardial performance index (Tie index) for early detection of cardiac affection in these patients.

Chapter (١):

# DIABETES MELLITUS

## ➢ Definition:

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, ٢٠١٣)***. It is the most common endocrine – metabolic disorder of childhood and adolescence ***(Ayoola, ٢٠٠٨).***

Diabetes mellitus (DM) makes up a group of hormonal diseases characterized by alterations in carbohydrate, protein, and lipid metabolism that results in elevated levels of blood glucose. More than ٢٢٠ million people in the world have DM, and this number is expected to double by ٢٠٣٠**(*Padwal et al.*, *٢٠٠٥*).** DM affects virtually all organs in the body, including the macrovascular system (heart) and the microvascular system (eyes, nerves, kidney, and the periodontium in the oral cavity). Cardiovascular complications of diabetes are common and are a leading cause of death in individuals with diabetes ***(Junttila, ٢٠١٠).***

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## ➢ Classification:

WHO classified D.M. into clinical (normoglycemia, impaired glucose tolerance (IGT)/ impaired fasting glycemia (IFG), diabetes), and etiological types ***(ADA, ٢٠١٢)*** as shown in table (١).

**Table (١):** Etiological classification of diabetes mellitus ***(ADA, ٢٠١٢)***

I. Type ١ diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type ٢ 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:
١. Chromosome ١٢, HNF-١$\alpha$ (MODY٣)
٢. Chromosome ٧, glucokinase (MODY٢)
٣. Chromosome ٢٠, HNF-٤$\alpha$ (MODY١)
٤. Chromosome ١٣, insulin promoter factor-١ (IPF-١; MODY٤)
٥. Chromosome ١٧, HNF-١ß (MODY٥)
٦. Chromosome ٢, Neuro D١ (MODY٦)
٧. Mitochondrial DNA
٨. Others
B. Genetic defects in insulin action:
١. Type A insulin resistance
٢. Leprechaunism

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٣. Rabson-Mendenhall syndrome
٤. Lipoatrophic diabetes
٥. Others

C. Diseases of the exocrine pancreas:
١. Pancreatitis
٢. Trauma/pancreatectomy
٣. Neoplasia
٤. Cystic fibrosis
٥. Hemochromatosis
٦. Fibrocalculous pancreatopathy
٧. Others

D. Endocrinopathies:
١. Acromegaly
٢. Cushing's syndrome
٣. Glucagonoma
٤. Pheochromocytoma
٥. Hyperthyroidism
٦. Somatostatinoma
٧. Aldosteronoma
٨. Others

E. Drug- or chemical-induced:
١. Vacor
٢. Pentamidine
٣. Nicotinic acid
٤. Glucocorticoids
٥. Thyroid hormone
٦. Diazoxide
٧. ß-adrenergic agonists
٨. Thiazides
٩. Dilantin
١٠. $\alpha$-Interferon
١١. Others

F. Infections:
١. Congenital rubella
٢. Cytomegalovirus

٣. Others

G. Uncommon forms of immune-mediated diabetes:
   ١. "Stiff-man" syndrome
   ٢. Anti–insulin receptor antibodies
   ٣. Others

H. Other genetic syndromes sometimes associated with diabetes:
   ١. Down's syndrome
   ٢. Klinefelter's syndrome
   ٣. Turner's syndrome
   ٤. Wolfram's syndrome
   ٥. Friedreich's ataxia
   ٦. Huntington's chorea
   ٧. Laurence-Moon-Biedl syndrome
   ٨. Myotonic dystrophy
   ٩. Porphyria
   ١٠. Prader-Willi syndrome
   ١١. Others

IV. Gestational diabetes mellitus (GDM)

*HNF: hepatocyte nuclear factor, MODY: maturity onset diabetes of youth,*

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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, ٢٠١٢).***

**The vast majority of cases of diabetes fall into two broad etio-pathogenetic categories as shown in table (٢) *(ADA, ٢٠١٢)*:**

**Table (٢):** Clinical characteristics of type ١ diabetes, type ٢ diabetes in children and adolescents ***(ADA, ٢٠١٢)***

| **Characteristics** | **Type ١** | **Type ٢** |
|---|---|---|
| Age of onset | ٦ months to young adulthood | Usually pubertal (or later) |
| Onset | Most often acute, rapid | Variable, from slow, mild to severe |
| Genetics | Polygenic | Polygenic |
| Clinical presentation | Most often acute, rapid | Variable; from slow (often insidious) to severe |
| Autoimmunity | Yes | No |
| Ketosis | Common | Uncommon |
| Glycemia | High | Variable |
| Obesity | Population frequency | Increased frequency |
| Frequency (% of all diabetes in young people) | Usually ٩٠٪+ | Most countries < ١٠٪ (Japan ٦٠-٨٠٪) |
| Acanthosis Nigerians | No | Yes |
| Parent with diabetes | ٢-٤٪ | ٨٠٪ |



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## ❖ Type ١ Diabetes Mellitus

Type ١ diabetes accounts for only ٥-١٠٪ of those with diabetes, previously encompassed by the terms insulin-dependent diabetes or juvenile-onset diabetes ***(American Diabetes Association Committee, ٢٠٠٧).*** Type ١ is further classified to the following subtypes:

### ١. Type la (The autoimmune form):

This form of diabetes, which accounts for only ٥–١٠٪ of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type ١ diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of pancreatic ß-cells representing about ٩٠٪ of type ١ cases in Europe. The presence of other autoimmune disorders is highly raised ***(ADA, ٢٠١٢).***

### ٢. Type lb (The idiopathic form):

Smaller group of type ١ diabetic patients exhibit no evidence of autoimmunity and the cause of insulin deficiency remains undefined.This cases are categorized as type ١b diabetes or idiopathic type ١ DM and are relatively more common in African and Asian population.This category is heterogenous, and remain poorly understood at this time ***(Ali, ٢٠١٠).***

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### ٣. Type l c:

Another ١B subtype is the fulminant type ١ diabetes mellitus (FT١DM), which was first reported by Imagawa et al. in ٢٠٠٠, is thought to be a unique subtype of type ١B diabetes. The initial reports of FT١DM were exclusively in Japanese population and accounted for about ٢٠٪ of their T١DM ***(Imagawa et al., ٢٠٠٠; ٢٠٠٣)***. Outside Japan, ***Cho et al. (٢٠٠٧)*** reported prevalence for FT١DM of ٧,١٪ in the newly diagnosed Korean T١DM patients. However, epidemiological study of FT١DM is lacking in other Asian populations and its incidence and pathogenesis remain to be elucidated. While a search for FT١DM was reported to be negative in the Caucasian population, case reports on FT١DM had surfaced in different ethnic groups, predominantly from Asian origins ***(Jung et al., ٢٠٠٤; Taniyama et al., ٢٠٠٤; Moreau et al., ٢٠٠٨)***. However, the causative mechanism of FT١DM is currently unknown ***(Arai et al., ٢٠١١).***

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**Table (٣):** The clinical and biological characteristic of different subtypes of type ١ diabetes ***(Imagawa et al., ٢٠٠٠)***

| | **Type ١a** | **Type ١b** | **Type ١c** |
|---|---|---|---|
| Signs of anti-islet autoimmunity | + | - | - |
| Duration of symptoms Before diagnosis | ٨ months | ٧ months | < ١ week |
| Ketosis, ketoacidosis at diagnosis | frequent | frequent | Constant |
| Blood glucose levels at diagnosis | ↑↑ | ↑↑ | ↑↑↑ |
| $HbA_1c$ at diagnosis | ↑↑ | ↑↑ | Normal or slightly elevated |

## Incidence and prevalence:

In most western countries, type ١ diabetes accounts for over ٩٠٪ of childhood and adolescent diabetes, although less than half of individuals with type ١ diabetes are diagnosed before the age of ١٥ years ***(Thunander et al., ٢٠٠٨)***. Type ٢ diabetes is becoming more common in adolescents, particularly in the peripubertal period, and accounts for a significant proportion of youth onset diabetes in certain at risk populations ***(Liese et al., ٢٠٠٦)***.

In ٢٠٠٧, the total child population of the world (٠-١٤ years) was estimated to be ١,٨ billion, of whom ٠,٠٢٪ have diabetes. This means that approximately ٤٤٠،٠٠٠ children



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around the world have diabetes with ٧٠،٠٠٠ new cases diagnosed each year. This very large number of children needs help to survive with injections of insulin to live a full life without restrictions or disabling complications and without being stigmatised for their diabetes ***(Global IDF/ISPAD Guideline, ٢٠١١)***.

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 ١ diabetes is reported to be ٨-١٠ per ١٠٠ ٠٠٠ population per year in children aged <١٥ years.In Egypt, the prevalence rate of Type ١ DM among school children in Heliopolis district in Cairo was ١,٠٩/١٠٠٠ with male predominance and in El Manyal district, the prevalence was ١,١٢/١٠٠٠ school children with female predominance ***(Ismail et al., ٢٠٠٨).***

## Etiology and Pathogenesis of type ١ diabetes:

Type ١ 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 ***(Raha et al., ٢٠٠٩).***

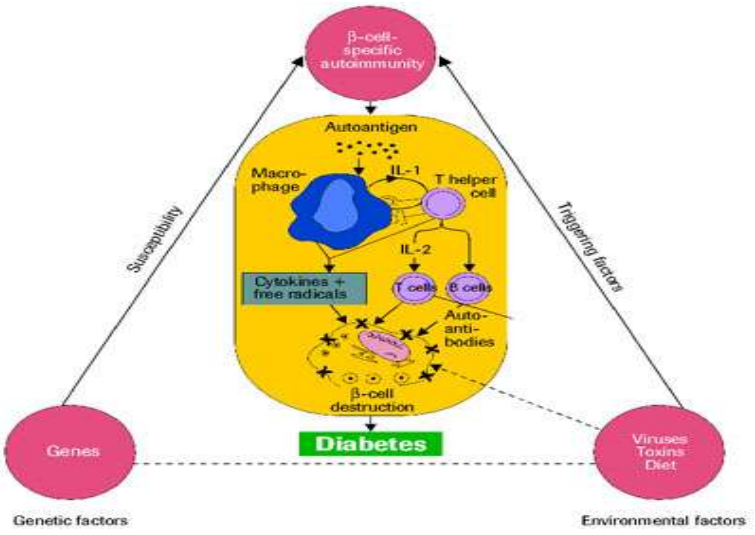


**Figure (١):** Pathogenesis of type ١ diabetes ***(Gillespie, ٢٠٠٦).***

**The development of type ١ DM has been divided into a series of stages**:

- Stage ١: Genetic predisposition.
- Stage ٢: Triggering of autoimmunity.
- Stage ٣: Development of a series of auto-antibodies.
- Stage ٤: Loss of B-cell function, as determined by intravenous glucose tolerance testing (metabolic defects).
- Stage ٥: Overt DM
- Stage ٦: Total or near total B-cell destruction with insulin dependence ***(Petrovsky and Schatz, ٢٠٠٣).***

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### ١) Stage I: Genetic Susceptibility

- Both the human leucocyte antigen (HLA) DRB١ and the HLA DQB١ gene loci play a role in the development and progression of autoimmune diabetes mellitus (T١DM) ***(Cejkova et al., ٢٠٠٨)***.

- Twin studies are based on comparison of the concordance (simultaneous occurrence) of a given disease among monozygotic (MZ; *i.e.*, identical) twins with the concordance among dizygotic (DZ; *i.e.*, fraternal) twins. MZ twins have identical genetic makeup, whereas DZ twins share an average of ٥٠٪ of their genes. Therefore, if the concordance is higher in the MZ twins compared with the DZ twins, it suggests that the disease has an inherited component. Several twin studies have shown a higher concordance rate of T١D in MZ twins when compared with DZ twins ***(Huber et al., ٢٠٠٨).***

There is T١DM is ١٥ times more likely in siblings of people with the condition; ie, the risk of developing T١DM in the general population is approximately ٠,٤٪, while for siblings of affected individuals, the risk is approximately ٦٪ ***(Redondo and Eisenbarth, ٢٠٠٢)***.Genes located within the HLA class II region on chromosome ٦p (IDDM١) account for approximately ٥٠٪ of genetic risk for T١DM. High-risk haplotypes associated with T١DM include: DQA١*٠٣٠١-DQB١*٠٣٠٢ with HLA DRB١*٠٤٠١, *٠٤٠٢ or *٠٤٠٥ alleles with HLA DRB١*٠٣٠١-DQA١*٠٥٠١-DQB١*٠٢٠١,٦ The insulin gene (INS) locus has



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