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# 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).***

Obesity is an important risk factor for diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease ***(Hubert et al., 1983);*** and is a strong predictor of increased morbidity and mortality ***(Calle et al., 1999).*** Visceral adipose tissue accumulation, through increased fatty acid production, may be involved in the genesis of insulin resistance, creating a milieu for the development of these disease ***(Frayn, 2000).***

Anthropometric measurements are often used as indirect measurements of visceral fat. Most widely used are waist circumference (WC) and waist-to-hip ratio (WHR). These measurement methods cannot differentiate between visceral fat tissue and subcutaneous fat tissue, but because their correlation with visceral fat tissue is quite good, they are often used as markers of visceral fat ***(Zamboni et al., 1998).***

Although anthropometric methods are frequently used today, they are inadequate for predicting cardiovascular risk increase, particularly in non-obese individuals. Therefore, search for convenience in clinical practice, low cost, and appropriate visceral fat tissue measurement methods are ongoing ***(Dilek et al., 2010).***

Ultrasonography has proved to be a suitable noninvasive and reliable tool for quantifying abdominal fat and has been found to be as useful as CT in evaluating abdominal fat ***(Hirooka et al., 2005).***

# Aim of Work

To assess the relationships between abdominal adiposity, insulin resistance, cardiovascular risk factors especially serum lipids and blood pressure in young type 1 diabetic patients.

## Chapter (1):

# Diabetes Mellitus

## Definition:

Diabetes 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 different organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(ADA, 2012).***

Type 1 diabetes (T1DM) is one of the most common childhood illnesses. The incidence of type 1 diabetes increasing rapidly worldwide ***(Devendra et al., 2004).***

### Classification:

The etiological classification recommended by the American diabetes association (ADA) and the World Health Organization (WHO) expert committee on the classification and the diagnosis is shown in table 1 with minor modification.

## Table (1): Etiological classification of DM

**I. Type 1**

β -cell destruction, usually leading to absolute insulin deficiency

A. e2Immune 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. Other

**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

**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 mellitus**

MODY: Maturity onset diabetes of the young; HNF−4α: Hepatocyte Nuclear Factor 4; NeuroD1: Neurogenic differentiation 1; KCNJ11 (Kir6.2): inward-rectifier potassium ion channel gene.

***(ADA, 2012)***

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

Type 1 diabetes

Type 2 diabetes

**Table (2): Characteristic feature of type 1 compare with type 2 diabetes in young people**

| Characteristics | Type 1 | Type 2 |
|---|---|---|
| **Age** | Throughout childhood | Pupertal or late |
| **Onset** | Most often acute ,rapid | Variable, from slow, mild, sever |
| **Genetics** | Polygenic | Polygenic |
| **Race / ethnics** | All groups, but wide variability of incidence | Certain ethnics groups are at particular risk |
| **Frequency** | Usually 90% | Most countries 10% |
| **Insulin dependence** | Permanent, total, sever | Uncommon ,but insulin required when oral hypoglycemic fail |
| **Insulin secretion** | Absent or very low | Variable |
| **Insulin sensitivity** | Normal | Decreased |
| **Autoimmunity** | Yes | No |
| **Ketosis** | Common | Rare |
| **Obesity** | No | Strong |
| **Acanthosis nigerias** | No | Yes |

***(Craig et al., 2009)***

**Type 1 is further classified to the following subtypes:**

**1-** Type 1a (The auto-immune form): 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-** Type 1b (idiopathic form): in which there is no evidence of auto-immunity, it represent about 10% of cases of type1 DM in Europe ***(Salma, 2003).***

Anew subtype of type 1 diabetes (fulminant type 1 diabetes) was established in 2000. It is syndrome characterized by a marked rapid and almost complete destruction of pancreatic B-cells. Several lines of evidence suggest that both genetic factors, such as human leukocyte antigen (HLA), and environmental factors, as viral infection, contribute to the development of this disease ***(Imaagawa and Hanafusa, 2006).***

**Clinical characteristics of fulminant type 1 diabetes:**

1- 20% of acute onset Japanese type 1 diabetes.
2- Duration of the disease less than 7 days.
3- High plasma glucose levels with near normal HbA1c.
4- Disease onset accompanied by ketoacidosis.
5- No C- peptide.
6- Elevated serum pancreatic enzyme level.
7- Negative Anti islent auto antibodies.

***(Imaagawa and Hanafusa, 2006)***

**Monogenic diabetes:**

**Definition**

Monogenic diabetes result from the inheritance of a mutation or mutations in a single gene. It may be dominant or recessively inherited or may be de novo mutation and hence a spontaneous case. In children, almost all monogenic diabetes results from mutations in genes that regulate beta–cell function although diabetes can rarely occur from mutation resulting in very sever insulin resistance ***(Musso et al., 2004).***

**Clinical presentation of monogenic diabetes:**

Clinical presentation in children when a diagnosis of monogenic diabetes should be considered and are discussed below and include:

1-neonatal diabetes and diabetes diagnosed within the first 6 months of life.

2- Familial diabetes with an affected parent.

3- Mild (5.5- 8.5 mmol/l) fasting hyperglycemia especially if young or familial.

4-Diabetes associated with extra pancreatic features.

***(Hattersley et al., 2009)***

## *Epidemiology of diabetes:*

In the western hemisphere DM is one of the most prevalent chronic diseases in childhood, whereas the incidence of T1DM in developing countries is significantly less than that in the western hemisphere. Epidemiological studies indicate that there is gradual but steady increase in the incidence of both T1DM and T2DM in both developed and developing countries. WHO estimates that by 2025 as many as 200-300 million people worldwide will have developed the disease ***(Hussain and Vincent, 2009).***

A recent study of incidence and prevalence of T1DM in children and adolescents in four Egyptian Governorates (Fayoum, Minofeya, North Sainai and Sues) was held by ***(Salem et al., 2007)***, showing a prevalence rate of 0.7/1000 and an incidence rate of 4.01/100.000.

### Age:

T1DM accounts for more than 90% of childhood and adolescent diabetes ***(ISPAD, 2009).***

Peaks of presentation occur in two age groups: at 5-7 yr of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the latter may correspond to the pubertal growth spurt induced by gonadal

steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). These possible cause-and-effect relationships remain to be proved ***(Alemzadeh and Wyatt, 2008).***

**Sex and socioeconomic status:**

Girls and boys are almost equally affected, there is no apparent correlation with socioeconomic status ***(Alemzadeh and Wyatt, 2008).***

**Race:**

Type 1 DM is more common among non-Hispanic whites, followed by African Americans and Hispanic Americans. It is comparatively uncommon among Asians ***(Hussain and Vincent, 2009)***.

**Season:**

Seasonal variation in the presentation of new cases is well described, with the peak being in the winter months ***(Ismail et al., 2008)***.

**Pathogenesis**

*The pathogenesis can be summarized as follows:*

In a genetically predisposed individual, environmental factors trigger an autoimmune process (activation of T lymphocytes reactive to islet cell antigens) that leads to

destruction of islet cells and insulin deficiency (Figure 1) ***(Pitas, 2004).***

Many data suggest that T cells are the key players in the autoimmune attack of β-cells. Anti-islet T cells, both CD4 and CD8 T cells, have been identified in type 1 diabetic patients ***(Bluestone et al., 2010).***

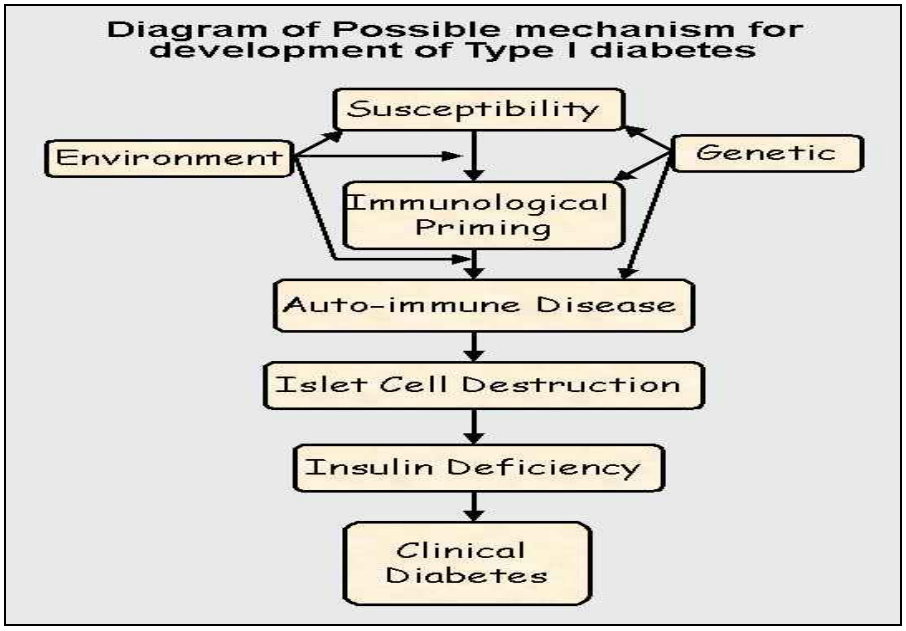


**Figure (1):** Possible mechanism for development of type 1 diabetes ***(Lamb, 2011).***

**Etiology:**

Type 1 diabetes is a multifactorial autoimmune disease with both environmental and genetic susceptibility ***(Cruz et al., 2004).***

***1. Genetic predisposing:***

Susceptibility is largely inherited, residing predominantly in the HLA genotypes DR & DQ, and to a lesser extent in a host of other genetic loci termed IDDM (insulin – dependant diabetes mellitus) susceptibility genes ***(Devendra et al., 2004)***.

Type I diabetes has become one of the most intensively studied polygenic disorder. The strongest associations with both susceptibility and protection from type 1 diabetes are HLD-DR and DQ molecules:

1. The inheritance of HLA-DR3 or DR4 antigens increases the risk of development of type IDM 2-3 folds. The inheritance of both increases the risk about 6-10 folds.
2. The homozygous absence of aspartic acid at position 57 of the HLA-DQ B-chain confers about 100 folds relative risk for developing type IDM.
3. The presence of arginin at position 52 of the HLA-DQ B-chain confers marked susceptibility to type IDM.

4. The inheritance of certain genotype HLA-DQ B1*D201, DQ A1*05/DQB1*0302-DQA1*03 carry the 10 times more frequency insulinitis than in children with other genotypes ***(Rodriguez et al., 2007)***.

In the higher incidence countries the risk to relatives of developing disease when a member of the family has type 1 diabetes are as follows:

- Risk to child/adolescent of a father with type 1 DM=7%.
- Risk to child/ adolescent of a mother with type 1DM=2%.
- Risk to identical twin of a child with type 1 DM = 36%.

For a sibling, the risk is approximately 4% by the age of 20 years and 9.6% by the age of 60 years ***(Steek et al., 2005),*** compared with 0.5% for the population ***(ISPAD, 2007).***

**II. Environmental factors:**

The increasing incidence of type IDM strongly suggests that environmental factors are very important. A leading hypothesis (hygienic hypothesis) is that the increase may be attributable to lack of childhood infections ***(Bach, 2002)***.

**These factors are:**

***1. Viral infection:***

Epidemiologic studies and experimental data obtained in animal models suggest the pathological role of certain viruses,

such as enteroviruses, as precipitating agents ***(Hober and Sauter, 2010).***

Recent molecular studies have considerably strengthened this hypothesis by showing that enterovirus genome is present in blood of newly diagnosed type 1 DM patient ***(Salminen et al., 2004)***.

Studies also suggest that maternal EV and rubella virus infections during pregnancy will increase the risk of type IDM in children ***(Otonkoski et al., 2004)***.

***2. Seasonal Factors:***

Newly recognized cases appear with greater frequency in the autumn and winter months in the northern and southern hemispheres ***(ISPAD, 2007)***. Attempts to link this with the incidence of mumps or infections have not been successful ***(Sperling, 2004)***.

***3. Dietary factors:***

1. Cow's Milk: feeding cow's milk to animal models of type I DM has been associated with the development of diabetes in these animals. The role of cow's milk in human type 1 DM is controversial. The likely mechanism is the molecular mimicry between a 17-amino acids peptide of