INTRODUCTION

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, 2008a)***.

Type 1 DM can occur at any age. It occurs most commonly in juveniles but can also occur in adults, especially in those in their late 30s and early 40s ***(Philippe et al., 2011).***

More than 180 million people worldwide have diabetes mellitus, and the number of diabetes patients is estimated to be doubled by 2030 ***(Ikuyo et al., 2011).***

It is a complex autoimmune disease affecting more than 30 million people worldwide. It is caused by a combination of genetic and non-genetic factors, leading to immune destruction of insulin-secreting islet cells ***(Abdulmoein et al., 2011).***

Morbidity and mortality in type 1 diabetic patients are derived mainly from advanced microvascular, neuropathic and macrovascular complications ***(Mohammadi et al., 2009)***. The development of such complications is related to the duration of diabetes and the degree of glycemic control. Dyslipidemia is a significant coronary artery disease (CAD) risk factor, which is

the leading cause of death in patients with type-1 diabetes ***(Adak and Shivapuri, 2010)***.

Type 1 diabetes is also associated with accelerated atherosclerotic complications. In a multicenter study, cardiovascular disease was ascertained to be the cause of death for 44% of the type 1 diabetic patients, followed by renal disease with a mortality of 21% ***(Morrish et al., 2001).***

Persistent hyperglycaemia causes glycosylation of all proteins, especially collagen cross linking and matrix proteins of arterial wall. This eventually causes endothelial cell dysfunction, contributing further to atherosclerosis. The prevalence of dyslipidemia in diabetes mellitus is 95%. The dyslipidemia is a major risk factor for coronary heart disease (CHD). Thecardiovascular disease is a cause of morbidity and mortality in patients with diabetes mellitus because of disturbance in lipoproteins ***(Khursheed et al., 2011)***.

Oxidized LDL has been implicated as a major factor in the atherosclerotic process in humans and in animal models because of its biological effects on endothelial cells, macrophages and smooth muscle cells ***(Gomes et al., 2005).***

A number of studies suggest the Ox-LDL is a more potent pro-atherosclerotic motivator than the native unmodified LDL. Ox-LDL has been observed to be increased in diabetic patients and this may contribute to the increased atherogenesis in diabetes,

regardless of normal lipid levels. Endothelium exposed to Ox-LDL develops alterations such as early signs of injury in the form of apoptosis. The oxidized low density lipoprotein (Ox-LDL) levels have been regarded as one of the independent determinants of intima media thickness (IMT) of the common carotid artery, a surrogate marker of atherosclerosis. Ox-LDL induces foam cell formation from macrophages that plays a key role in early atherogenesis. Oxidation of LDL occurs primarily in the vessels wall, thus activating many inflammatory and atherogenic reactions ***(Aqeela et al., 2010*)**.

Immune mechanisms have been suggested to play a key role in atherosclerosis development. Several lines of evidence support the concept that oxidized LDL may be a key antigen in this process. T-cell clones responsive to Ox-LDL have been isolated from human lesions. Soluble form of cell adhesion molecules intercellular adhesion molecule-1 [ICAM-1], can be detected in serum, and these molecule recently have been detected in several components of human atheroma; in addition, cross-sectional and prospective data suggest that soluble form of these protein are elevated among patients with diverse manifestations of atherosclerosis ***(Johannes et al., 2001).***

Inflammatory mediators may be pathogenic by inducing vascular endothelial dysfunction. Leukocyte recruitment and adhesion to vascular endothelium, mediated by cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), play an important role in the development of atherosclerosis. In

several studies have shown that circulating ICAM-1 may serve as a molecular marker for atherosclerosis and development of CHD. In vitro studies show that Ox-LDL induces dose dependent expression of ICAM-1 on endothelial cells and stimulates ICAM-1-dependent adhesion of monocytes ***(Hoogeveen et al., 2007).***

Aim of the Work

This study aim to assess the level of oxidized low density lipoprotein (Ox-LDL) in children and adolescents with type 1 diabetes milletus, investigate the association of the marker level with the occurrence and severity of both micro-vascular and macro-vascular complications, and investigate the relation between intracellular adhesion molecules and Ox-LDL in IDDM.

DIABETES MELLITUS

Definition of Diabetes:

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, 2014)***.

Hyperglycemia is the landmark of this metabolic syndrome and is the parameter most closely monitored to make diagnosis and to judge therapy ***(ADA, 2004a)***.

Epidemiology of diabetes mellitus:

Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and continues to increase in numbers and significance, as changing life styles lead to reduced physical activity, and increased obesity. Estimates of the current and future burden of diabetes are important in order to allocate community and health resources, and to emphasize the role of lifestyle, and encourage measures to counteract trends for increasing prevalence ***(Shaw et al., 2010)***.

The economic and social costs of diabetes are enormous, both for health care services and through loss of productivity. In developed countries, 10% or more of the total health budget is spent on the management of diabetes and its complications ***(Zimmet et al., 2003)***.

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 ***(Sarah et al., 2004)***.

Criteria for the diagnosis of diabetes mellitus:

The current diagnostic criteria for diabetes as stated by the ***American Diabetes Association (ADA), 2012***:

Criteria for the diagnosis of diabetes:

1- Glycated hemoglobin (HBA1c) ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

Or

2- Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

Or

3- 2-hours (h) plasma glucose (PG) ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Or

4- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

- In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

(ADA, 2012)

Prior Expert Committees have not recommended use of the hemoglobin A1c for diagnosis of diabetes, in part due to lack of standardization of the assay. However, hemoglobin A1c assays are now highly standardized so that their results can be uniformly applied both temporally and across population. In their recent report, an International Expert Committee, after an extensive review of both established and emerging epidemiological evidence, recommended the use of the A1c test to diagnose diabetes, with a threshold of ≥6.5%, and American Diabetes Association (ADA) affirms this decision. The diagnostic A1c cut point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for FPG and 2h- PG ***(International Expert Committee, 2009)***.

Categories of increased risk for diabetes:

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus, recognized an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered normal. These people were defined as having impaired fasting glucose (IFG)

[fasting plasma glucose (FPG) levels 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)], or impaired glucose tolerance (IGT) [2-h values in the oral glucose tolerance test (OGTT) of 140 mg/dl (7.8 mmol/l) to 199 mg/dL (11.0 mmol/l)]. Individuals with IFG and/or IGT have been referred to as having pre-diabetes, indicating the relatively high risk for the future development of diabetes ***(Expert Committee, 1997 and 2003)***.

The original criterion for diagnosis of IFG was lowered by the ADA from 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.6 mmol/l) to increase sensitivity (with an acceptable drop in specificity) for persons with an increased diabetes risk. However, the World Health Organization (WHO) and many other diabetes organizations did not adopt this change in the definition of IFG ***(Expert Committee, 2003)***.

When recommending the use of the hemoglobin A1c to diagnose diabetes in its 2009 report, the International Expert Committee stressed the continuum of risk for diabetes with all glycemic measures and did not formally identify an equivalent intermediate category for hemoglobin A1c. The group did note that those with hemoglobin A1c levels above the laboratory "normal" range but below the diagnostic cut point for diabetes (6.0 to <6.5%) are at very high risk of developing diabetes ***(International Expert Committee, 2009)***. Indeed, incidence of diabetes in people with A1c levels in this range is more than 10 times that of people with lower levels ***(Sato et al., 2009)***.

Categories of increased risk for diabetes:

- FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) [IFG].
- 2-hours PG in the 75-g OGTT 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l) [IGT].
- A1c 5.7-6.4%.
- For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range ***(ADA, 2012)***.

Classification of diabetes:

The etiologic classification of diabetes mellitus currently recommended by the WHO and the ADA is presented in table (3). This classification differs considerably from the previously recommended classification, which used the term insulin-dependent diabetes and non-insulin dependent diabetes ***(ADA, 2008b)***.

Etiologic classification of diabetes mellitus:

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-1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4α (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-β (MODY5)
6. Chromosome 2, NeuroD1 (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. γ-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 ataxia
6. Huntington chores
7. Laurence-Moon-Biedl syndrome

8. Myotonic dystrophy

9. Porphyria

10. Prader-Willi syndrome

11. Others

IV. Gestational diabetes mellitus

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, 2011a)***.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In one category, type 1 diabetes which accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes or juvenile-onset diabetes, the cause of it is an absolute deficiency of insulin secretion. In the other, much more prevalent category, type 2 diabetes which accounts for 90-95% of those with diabetes previously referred to as non-insulin-dependent diabetes or adult-onset diabetes, the cause of it is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response ***(ADA, 2008a)***.

Type1 diabetes is a complex autoimmune disease that is untimely caused by the destruction of insulin producing pancreatic B- cells by auto reactive T cells ***(Diana et al., 2011)***.

Type 1diabetes is one of the most common chronic diseases in childhood with 480,000 children estimated affected globally. The incidence is increasing at 3% per year and annually 76,000 children aged less than 15 years old develop Type 1 Diabetes worldwide ***(International diabetes federation 2011)***.

Type 1 Diabetes Mellitus is the most frequent endocrinology disease in children. The chronic course of the disease and life-long substitution of insulin- therapy that must be coordinated with the food, physical activity and the results of monitoring blood glucose are factors that make life of these children and their families very difficult ***(Abusaad, 2014)***.

This condition is characterized by sever insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life therefore it is termed insulin dependent diabetes mellitus. The onset occurs predominantly in childhood but it may come at any age. Hence such terms as Juvenile diabetes and brittle diabetes have been abandoned in favor of type1 diabetes mellitus ***(Petrovsky et al., 2003)***.

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

	Type 1 diabetes (T1D)	**Type 2 diabetes (T2D)**
Age of onset	Commonly occur in childhood and adolescents	Mostly in adults
Onset	Most often acute, rapid	Gradual
Genetics	Polygenic	Polygenic
Prevalence	5-10% of those with diabetes	90-95% of those with diabetes
Insulin secretion	Low or absent	Variable, may be normal, decreased or increased
Insulin sensitivity	Normal	Decreased
Insulin dependence	Dependent on insulin for survival	Initially absent in most cases
Autoantibodies	Present in 85-90% of individuals with T1D	Absent
Ketosis	Common	Rare
Obesity	Rare	Common

(ADA, 2013a)