INTRODUCTION

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is a complex matter and requires that many issues, beyond glycemic control, should be addressed ***(Tasali et al., 2008).***

Diabetes mellitus is commonly associated with both microvascular and macrovascular complications increasing morbidity and reducing life expectancy. There is therefore more and more interest in identifying diagnostic and therapeutic strategies to reduce or delay the possible onset of these complications ***(Giugliano et al., 2009).***

Diabetic retinopathy (DR), one of the main causes of blindness in adults, is a relatively common complication, often causing no symptoms or only mild vision problems ***(Cerbone et al., 2009).***

Despite advances in treatment such as laser photocoagulation, intravitreal injection of anti- VEGF (Vascular Endothelial Growth Factor) or vitreous surgery, vision does not improve significantly in many and in some, vision continues to decline ***(Aiello et al., 1997).***

The most commonly accepted pathophysiological model for this visual loss is attributed to vascular change (microvascular theory) in the retina, particularly in retinal capillaries: capillary

dilatation and increased permeability leading to microaneurysms, haemorrhages, retinal exudates, endothelial cell proliferation and so on the other pathophysiological model, somewhat less investigated, is the neurodegenerative theory ***(Barber, 2003).***

The neurodegenerative changes are apoptosis of several neuronal cells including ganglion, amacrine, horizontal, Muller and photoreceptor cells; these changes probably precede microvascular changes ***(Lieth et al., 2000).***

These changes explain some of the functional deficits in vision occurring early in the course of the disease. These changes have been studied with neurophysiological, psychometric, histopathological and biochemical experiments, and are supported by the electrophysiological and clinical evidence such as pattern electroretinogram, contrast sensitivity and colour vision ***(Greenstein et al., 1990).***

The diagnostic strategies for early detection of DR are of high priority to avoid or prevent loss of vision in patients with diabetes. Ophthalmoscopy, fundus photography and, if necessary, fluorescein angiography are the common techniques used to diagnose DR ***(McIntosh et al., 2000).***

A sensitive, non-invasive and high-resolution method for examining ocular tissue, optical coherence tomography (OCT), has been proposed for early detection of DR; this technique is able to detect even very small changes in the retinal layers, therefore improving the diagnosis and management of DR ***(Lang, 2007).***

In patients with macular edema, it is generally accepted that OCT is a more sensitive technique for measuring retinal thickness (RT) and volume ***(Panozzo et al., 2003),*** while the current gold standard for the identification of the incipient lesions related to subclinical macular edema or without loss in cells of the retinal layer is fundus photography ***(McIntosh et al., 2000).***

Several studies have reported OCT-documented alterations in the RT of patients with diabetes with DR, although no unanimous results have been obtained ***(Browning et al., 2008).***

Conversely, only a few authors have published data reporting that OCT is useful in the early stages of DR, as in the presence of subclinical edema ***(Schaudig et al., 2000).***

Optical coherence tomography (OCT) provides reliable, reproducible, and objective retinal images and permits quantitative assessment in diabetic macular oedema ***(Forooghian et al., 2008).***

Spectral domain OCT is a newer-generation high-resolution OCT with the advantages of high-speed data acquisition, three-dimensional reconstruction of acquired retinal images, and improved visualisation of retinal architecture, layer by layer ***(Schmidt-Erfurth et al., 2005).***

AIM OF THE WORK

The aim of the present study is:

1. To detect early microvascular changes in patients with type 1 DM before the presence of frank clinical retinopathy.
2. To assess the relationship between presence of early signs of retinopathy and any associated microvascular complications.
3. To determine risk factors of microangiopathy as age, duration of diabetes, anthropometric measurements, BMI, pubertal stage, glycemic control and total serum cholesterol.

DIABETES MELLITUS

Definition

Diabetes mellitus is a group of metabolic diseases characterised 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. If ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly ***(Duabetes Care, 2009).***

Table (1): Criteria for the diagnosis of diabetes.

1. A1C ≥6.5 percent. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
2. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an 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).

A1C: glycated hemoglobin; NGSP: national glycohemoglobin standardization program; DCCT: diabetes control and complications trial; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

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

(ADA, 2011).

Pathogenesis of type 1 diabetes

- Individuals have an absolute deficiency of insulin secretion and are prone to ketoacidosis
- Most cases are primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic beta cells are destroyed ***(Gepts, 1965).***
- Serological markers of an autoimmune pathologic process, including islet cell, GAD, IA-2, IA- 2β, or insulin autoantibodies, are present in 85-90% of individuals when fasting hyperglycemia is detected ***(Sabbah et al., 2000).***
- Combined testing for ICA and GAD antibodies could provide a highly discriminatory ascertainment of risk for type 1 diabetes in sibilings of diabetic patients ***(El-Habashy et al., 2002).***
- Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; in a recent metaanalysis more than 40 distinct genomic locations provided evidence for association with T1D ***(Barrett et al., 2009).***

  HLA genes having the strongest known association, there is linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible or protective haplotypes ***(Erlich et al., 2008).***
- Individuals at increased risk of developing type 1 diabetes can often be identified by measurement of diabetes associated autoantibodies, genetic markers and intravenous glucose tolerance testing.

- The environmental triggers (chemical and/or viral) which initiate pancreatic beta cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms.

  Enterovirus infection has been associated with development of diabetes associated autoantibodies in some populations ***(Sadeharju et al., 2003),*** and enteroviruses have been detected in the islets of individuals with diabetes ***(Richardson et al., 2009).***

  These viruses are known to induce pancreatitis especially the coxasackie viruses, and it has also been shown that these viruses can infect human beta cells in vitro. Some studies reported coxasackie B4 strain was isolated from the pancreas of child who died of diabetic ketoacidosis. Demonstration of the virus from pancreatic islets would considerably strengthen the enteroviruses hypothesis and would help to understand the mechanism of how the virus would induce beta cell damage ***(Monir et al., 2005).***

- In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of diabetic ketoacidosis (DKA) at presentation ***(Dunger et al., 2004).***

- When the clinical presentation is typical of type 1 diabetes (often associated with DKA) but antibodies are absent, then the diabetes is classified as Type 1B (idiopathic). Most are of African or Asian ancestry, however other forms of diabetes should also be considered as shown in Table 2.

Table (2): Aetiological classification of disorders of glycemia

I. Type 1

β -cell destruction, usually leading to absolute insulin deficiency

A. Immune 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. Chromosome 7, KCNJ11 (Kir6.2)
9. 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. 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
4. Polyendocrine autoimmune deficiencies APS I and II

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

(Ispad, 2009).

Incidence rate

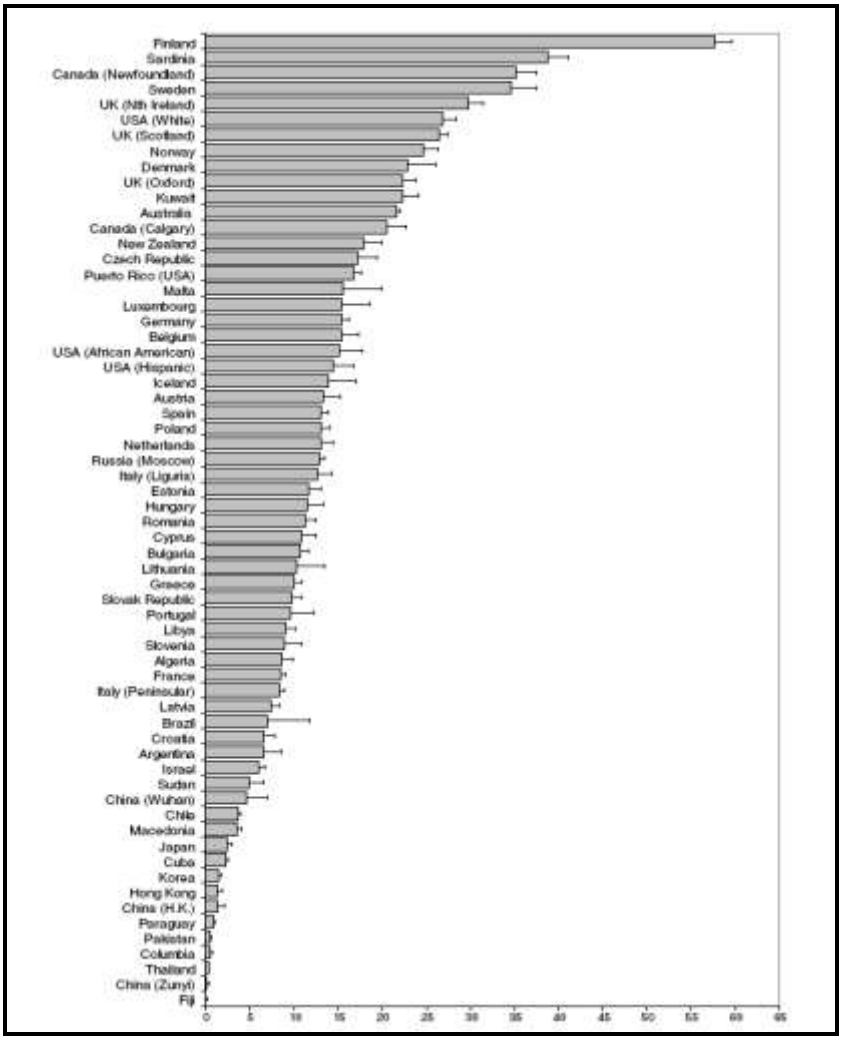

Fig. (1): Mean Annual Incidence Rates for Type 1 Diabetes (0–14 year age group) Comparing Different Countries in the World ***(Ispad, 2009).***

Epidemiology of type 1 diabetes

- In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years ***(Thunander et al., 2008).***

Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at risk populations ***(Pinhas-Hamiel and Zeitler, 2005).***

- Epidemiological incidence studies define the 'onset of type 1 diabetes' by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis.
- ***Salem et al. (2007)*** hold a more recent study of incidence and prevalence in children and adolescents in four Egyptian Governorates (Fayoum, Minofeya, North Sainai and Suez). Preliminary results showed that its prevalence was 0.7/1000 and its incidence of 4.01/100.000.
- Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations. Mean annual incidence rates for childhood type 1 diabetes (0–14 years age group) comparing different countries of the world are shown in Figure 1 (0.1 to 57.6 per 100,000) ***(Kawasaki et al., 2006).***
- In Europe incidence rates show a close correlation with the frequency ofHLA susceptibility genes in the general population.
- In Asia, the incidence of type 1 diabetes is extremely low: China 0.1 per 100 000, Japan 2.4 per 100,000 ***(Kawasaki, 2006).*** and has a different and unique HLA association compared with Caucasians.

  In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan, which represents approximately one third of cases of type 1 diabetes ***(Urakami et al., 2008).***

- The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low risk HLA genotypes in some populations ***(Fourlanos et al., 2008).***

- Gender differences in incidence are found in some, but not all, populations ***(Weets et al., 2004).***

- A well documented rise in the incidence has been noted in many countries, and in some reports there has been a disproportionately greater increase in those under the age of 5 years ***(Patterson et al., 2009).***

- A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months ***(Levy-Marchal et al., 1995).***

- Despite familial aggregation, which accounts for approximately 10% of cases of type 1 diabetes ***(Harris et al., 2003),*** there is no recognisable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is about 36% (60); for a sibling the risk is approximately 4% by age 20 years ***(Steck et al., 2005),*** and 9.6% by age 60 years; compared with 0.5 % for the general population. The risk is higher in siblings of probands diagnosed at younger age.

- Type 1 diabetes is 2–3 times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%)

Table (3): Clinical characteristics of type 1 diabetes, type 2 diabetes and Monogenic diabetes in children and adolescents.

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except Glucokinase and neonatal diabetes
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in glucokinase)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal diabetes, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% Japan 60-80%)	?1-3%
Parent with diabetes	2-4%	80%	90%

(Ispad, 2009).

Table (4): Complications of type 1 diabetes.

▶ **Acute:**
▪ Ketosis. ▪ Ketoacidosis. ▪ Hypoglycaemic episodes. ▪ Infections.
▶ **Chronic**
Microvascular disease: ▪ Retinopathy, cataract. ▪ Nephropathy. ▪ Neuropathy. ▪ Polyneuropathy, mononeuropathy, autonomic dys-function. - Foot ulcers (vascular disease is also a cause). - Impotence.
▶ **Macrovascular disease:**
▪ Coronary heart disease. ▪ Cerebrovascular disease. ▪ Peripheral vascular disease. - Skin (infections, mycosis, lipodystrophy). - Psychosocial, depression.

(Salma, 2003)

Microvascular complications

The long-term vascular complications of diabetes include retinopathy, nephropathy, neuropathy and macrovascular disease. The outcomes are:

- Visual impairment and blindness due to diabetic retinopathy
- Renal failure and hypertension due to diabetic nephropathy
- Pain, paraesthesiae, muscle weakness and autonomic dysfunction due to diabetic neuropathy
- Cardiac disease, peripheral vascular disease and stroke due to macrovascular disease

Clinically evident diabetes-related vascular complications should be rare in childhood and adolescence.

However, early functional and structural abnormalities may be present a few years after the onset of the disease.

Childhood and adolescence is a period during which intensive education and treatmentmay prevent or delay the onset and progression of complications ***(Dcct, 1994).***

There has been a declining incidence of complications reported in many areas with specialised clinics.

This has occurred over a period of time during which there have been major changes in diabetes management, identification of putative risk factors, and the advent of regular screening for complications. There is no evidence that this is a world-wide

occurrence: in areas where health care is not optimal, a greater risk of complications will remains.

Microvascular and macrovascular complications associated with diabetes in children and adolescents

Table (5): Screening, risk factors and interventions for vascular complications: the levels of evidence for risk factors and interventions pertaining to adult studies, except for improved glycaemic control.

	When to commence screening?	Screening methods Screening methods	Risk factors Risk factors	Potential intervention
Retinopathy	Annually from age 11 years with after 2 years duration and from 9 years with 5 years duration **(E)**	Fundal photography or mydriatic ophthalmoscopy (less sensitive) **(E)**	Hyperglycaemia **(A)** High blood pressure **(B)** Lipid abnormalities **(B)** Higher BMI **(C)**	Improved glycaemic control **(A)** Laser therapy **(A)**
Nephropathy	Annually from age 11 years with 2 years duration and from 9 years with 5 years duration **(E)**	Urinary albumin/creatinine ratio or first morning albumin concentration **(E)**	High blood pressure **(B)** Lipid abnormalities **(B)** Smoking **(B)**	Improved glycaemic control **(A)** ACEI and AIIRA **(A)** Blood pressure lowering **(B)**
Neuropathy	Unclear	History and physical examination	Hyperglycaemia **(A)** Higher BMI **(C)**	Improved glycaemic control **(A)**
Macrovascular disease	After age 12 years **(E)**	Lipid profile every 5 years, blood pressure annually **(E)**	Hyperglycaemia **(A)** High blood pressure **(A)** Lipid abnormalities **(B)** Higher BMI **(B)** Smoking **(B)**	Improved glycaemic control **(A)** BP control **(B)** Statins **(A)**

(Ispad, 2009).

Risk factors for the development of complications

Longer duration of diabetes, older age and puberty are risk factors for complications.

The prepubertal years of diabetes duration have a significant lesser impact especially further from the onset of gonadarche.

For the same diabetes duration, age and puberty increase the risk for retinopathy ***(Donaghue et al., 2005).***

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria. The evidence for the effect of smoking on retinopathy is less clear. Type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality ***(Gay et al., 1992).***

Hypertension has a greater impact on cardiovascular disease in diabetic patients than in non-diabetic individuals Blood pressure control (<130/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes.

Dyslipoproteinaemia is associated with microalbuminuria and retinopathy ***(Lyons et al., 2004).***

This included higher total and LDL cholesterol and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apoprotein B in men. Family history of complications increases the risk for nephropathy ***(Seaquist et al., 1989)*** and retinopathy ***(Soergel, 1997).***

Higher body mass index (BMI) is a risk factor for retinopathy neuropathy microalbuminuria and cardiovascular disease Life style issues: sedentary men with diabetes have higher mortality than active individuals ***(Moy et al., 1993).***