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منسّق:تباعد الأسطر: تام 3.14 نقطة، العرض: تماماً 66.1 سم

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 ***(American Diabetes Association, 2012).***

Type 1 diabetes mellitus is caused by deficiency of insulin secretion due to pancreatic β-cell damage ***(Atkinson and Eisenbarth, 2001)***. It is the most common endocrine-metabolic disorder of childhood and adolescence (90% of cases) and accounts for only 5-10% of all cases of diabetes, with important consequences for physical and emotional development ***(Wyatt, 2008)***.

Diabetes causes a number of complications either; acute complications including diabetic ketoacidosis, hyperglycemic hyperosmolar state, hypoglycemia and respiratory infections ***(American Diabetes Asssociation, 2006)***, in addition to chronic complications including micro-vascular diseases; diabetic retinopathy ***(Ciulla et al., 2003)***, diabetic neuropathy ***(Vinik et al., 2003)***, diabetic nephropathy ***(Gross el al., 2005)*** and diabetic cardiomyopathy ***(Bell, 2003)*** while macro-vascular diseases are coronary artery disease, ischemic stroke, peripheral

vascular disease and diabetic myonecrosis ***(Reyes-Balaguer et al., 2005)*** as well as diabetic foot ***(Lavery et al., 2003).***

A common approach for the prevention and treatment of diabetes complications relies on the understanding of their complex pathophysiology ***(Fadini et al., 2007)***. The risk of developing micro-vascular complications is related mainly to the duration of diabetes and degree of glycemic control achieved over time ***(Acerini et al., 2008)***. Angiogenesis, the formation of new blood vessels, is a complex process and involves the survival, activation, proliferation, differentiation, migration and reorganization of endothelial cells ***(Folkman , 1995)***. In diabetes, angiogenesis is disturbed, contributing to proliferative retinopathy, nephropathy and neuropathy. Hyperglycemia, hypertension, dyslipidemia, adiposity, inflammation and oxidative stress may promote vascular complications ***(Jenkins et al., 2004)***.

Endothelial dysfunction is implicated in the pathogenesis of diabetes and atherosclerosis ***(Hadi and Suwaidi, 2007)***. Endothelial monocyte-activating polypeptide II (EMAP II) is a multifunctional polypeptide with proinflammatory and antiangio-genic activity, which exerts pleiotropic effects on endothelial cells, monocytes and neutrophils. EMAP II was first isolated from supernatants of cultured murine methylcholanthrene A-induced fibrosarcoma cells and is closely related or identical to the p43 auxiliary protein of the multisynthase complex, which is involved in protein synthesis ***(Kao et al., 1992)***.

EMAP II is synthesized as a 34 kDa precursor molecule (proEMAP) and enzymatically cleaved to produce a biologically active 22 kDa mature polypeptide, which has been isolated and characterized ***(Tas and Murray, 1996)***. In vitro, EMAP II induces procoagulant activity, increased expression of E- and P-selectins and tumor necrosis factor receptor-1, blocks adhesion of endothelial cells to fibronectin as well as matrix assembly by binding to α5β1 integrin ***(Schwarz et al., 2005)***. EMAP II is also chemotactic for monocytes and neutrophils. It induces an acute inflammatory reaction and tumour regression in vivo ***(Murray et al., 2004)***.

Recent evidence suggests that EMAP II can induce apoptosis in cultured endothelial cells and inhibits proliferation, vascularization and neovessel formation ***(Berger et al., 2000)***. EMAP II has been shown to suppress tumor growth by its potent anti-angiogenic properties ***(Schwarz and Schwarz, 2004)*** and it reduces vascular endothelial growth factor (VEGF) expression, which itself facilitates tumor growth through induction of angiogenesis ***(Awasthi et al., 2009)***. Although EMAP II could reflect an endothelial dysfunction and disturbed angiogenesis in patients with type 1 diabetes, its role in relation to diabetic vascular complications has not been explored.

AIM OF THE WORK

The aim of this study was to determine EMAP II levels in children and adolescents with type 1 diabetes mellitus as a potential marker for diabetic vascular complications and assess its relation to the clinicopathological characteristics of patients and glycemic control.

Chapter 1

DIABETES MELLITUS

Diabetes is a consequence of immune-mediated destruction of pancreatic B-cells in a genetically predisposed individual ***(Balkau and Eschwege, 2003)***. Hyperglycemia is the land mark of this metabolic syndrome and is the parameter most closely monitored to make diagnosis and to judge therapy ***(The Expert Committee on the diagnosis and classification of DM, 2004).***

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type-2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response ***(American Diabetes Association, 2004).***

The risk of developing microvascular complications is related mainly to the duration of diabetes and degree of glycemic control achieved over time. Genetic factors also may influence the risk of complications. These complications are mainly renal microvascular complication (microalbuminurea or

diabetic nephropathy), retinopathy and neuropathy (peripheral or autonomic) ***(Robert et al., 2007)***.

Morbidity and mortality from metabolic derangement and from long term complications that affect small and large vessels result in retinopathy, nephropathy, ischemic heart disease and arterial obstruction with gangrene of extremities makes diabetes cover a wide range of heterogenous diseases ***(Kuzuya et al., 2002)***.

Diagnosis of diabetes in childhood and adolescence ***(International Diabetes Federation, 2011)*:**

- Diabetes in children usually presents with characteristic symptoms such as polyuria, polydipsia, blurring of vision, and weight loss, in association with glycosuria and ketonuria.
- In its most severe form, ketoacidosis or rarely a non-ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death.
- The diagnosis is usually confirmed quickly by measurement of a marked elevation of the blood glucose level. In this situation if ketones are present in blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycemia may be dangerous in allowing ketoacidosis to evolve rapidly.

منسّق:علامات الجدولة: ليس عند 72.1 سم

- In the absence of symptoms or presence of mild symptoms of diabetes, hyperglycemia detected incidentally or under conditions of acute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes.

The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or 2 hour post-prandial blood glucose levels and/or an oral glucose tolerance test (OGTT). An OGTT should not be performed if diabetes can be diagnosed using fasting, random or post-prandial criteria as excessive hyperglycemia can result. It is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence. If doubt remains, periodic re-testing should be undertaken until the diagnosis is established. Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms ***(Craig et al., 2009)***.

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Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods given in Table 1.

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Table (~~1111~~): Criteria for the diagnosis of diabetes:

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- HbA_{1c} > 6.5%. The test should be performed in a laboratory using a method standardized to the DCCT assay.*

OR

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FPG (fasting plasma glucose) > 126 mg /dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

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- 2-h plasma glucose> 200 mg/dL (11.1mmol/L) during an OGTT. The test should be performed as described by the world health organization (WHO), using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.*
- **OR**

  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, result should be confirmed by repeat testing.

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(ADA, 2012)

Classification of diabetes:

Diabetes is not a single entity, but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance ***(Boyle and Zrebic, 2007)***. A classification of diabetes is presented in Table 2.

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Table (2222): Etiologic classification of diabetes mellitus

A. Type I-DM: Which is characterized by destructive lesion of pancreatic -cells by an autoimmune mechanism or unknown cause.	**B. Type II-DM:** This is characterized by combination of decreased insulin secretion and decreased insulin sensitivity (insulin resistance).
C. 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	**D. Genetic defects in insulin action** 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others
E. Diseases of the exocrine pancreas 1. Pancreatitis 2. Trauma / pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Haemochromatosis 6. Fibrocalculous pancreatopathy 7. Others	**F. Endocrinopathies** 1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Phaeochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others
G. 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	**H. Infections** 1. Congenital rubella 2. Cytomegalovirus 3. Others
I. 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	**J. 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
K. Gestational Diabetes.	

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)

منسّق:الإنجليزية (الولايات المتحدة الأمريكية)

منسّق:السويدية (السويد)

منسّق:البرتغالية (البرازيل)

منسّق:لون الخط: أسود، دون تمييز

منسّق:دون تمييز

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منسّق:دون تمييز

Different types of diabetes:

The differentiation between type 1, type 2 and monogenic diabetes has important implications for both therapeutic decisions and educational approaches. Regardless of the type of diabetes, however, the child who presents with severe fasting hyperglycemia, metabolic derangements and ketonaemia, will require insulin therapy initially to reverse the metabolic abnormalities ***(Silverstein et al., 2005)***.

منسّق: المسافة البادئة: قبل: 10.0 سم، معلقة: 36.0 سم، تعداد نقطي + المستوى: ١ + محاذاة عند: 36.0 سم + علامة جدولة بعد: 72.1 سم + مسافة بادئة: 72.1 سم، علامات الجدولة: 46.0 سم، جدولة قائمة + ليس عند 72.1 سم

- Measurement of diabetes associated autoantibody markers and/or hemoglobin A1c (HbA1c) may be helpful in some situations, however there is currently insufficient evidence to support the routine use of the HbA1c for the diagnosis of diabetes ***(American Diabetes Association, 2009)***.
- Measurement of fasting insulin or C-peptide may be useful in the diagnosis of type 2 diabetes in children. Fasting insulin and C-peptide levels are usually normal or elevated, although not as elevated as might be expected for the degree of hyperglycemia ***(American Diabetes Association, 2000)***. If patients are insulin treated, measuring C-peptide when the glucose is sufficiently high (>8 mmol/l) to stimulate C peptide will detect if endogenous insulin secretion is still occurring. This is rare outside the honeymoon period (2-3 years) in children with Type 1 diabetes.

The possibility of other types of diabetes should be considered in the child who has:

منسّق: المسافة البادئة: قبل: 10.0 سم، معلقة: 36.0 سم، تعداد نقطي + المستوى: ١ + محاذاة عند: 0 سم + علامة جدولة بعد: 36.0 سم + مسافة بادئة: 36.0 سم

- An autosomal dominant family history of diabetes.

- Associated conditions such as deafness, optic atrophy or syndromic features.
- Marked insulin resistance or require little or no insulin outside the partial remission phase.
- A history of exposure to drugs known to be toxic to beta cells or cause insulin resistance.

The characteristic features of youth onset type 1 diabetes in comparison with type 2 diabetes and Monogenic diabetes are shown in Table 3.

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Table (3333): 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 to severe in glucokinase)	Variable may be incidental(often insidious)
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%	1-3%
Parent with diabetes	2-4%	80%	90%

(Craig et al., 2009)

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Type 2 DM

Type 2 DM occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance ***(Druet et al., 2006)***. Thus, Type 2 DM is commonly associated with other features of the insulin resistance syndrome [hyperlipidemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, non-alcoholic fatty liver disease (NAFLD)] ***(Miller et al., 2007)***. Insulin secretion depends on disease status and duration, and can vary from delayed but markedly elevated in response to a glucose challenge, to absolutely diminished ***(Druet et al., 2006)***. Adults with symptoms have 50% reduction at the time of diagnosis, and may become insulin dependent within a few years ***(UKPDS Group, 1998).***

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Type 2 DM occur in youth most often during the second decade of life, with a mean age of diagnosis of about 13.5 years. This coincides with the peak of physiologic pubertal insulin resistance, which may lead to onset of overt diabetes in previously compensated adolescents. One third or more of newly diagnosed youth with type 2 DM presented with ketosis/ketoacidosis. This presentation is responsible for misclassification of type 2 DM patients as type 1 DM ***(Pinhas-Hamiel et al., 2007; Morales et al., 2004).***

Monogenic diabetes

Monogenic diabetes mellitus was originally described as a disorder with the following characteristics: onset before 25 years of age, autosomal dominant inheritance, nonketotic diabetes mellitus ***(Murphy et al., 2008; Owen and Hattersley, 2001)***. These classical definitions given to MODY are no longer very helpful as type 2 diabetes occurs in children and will often meet all these criteria ***(American Diabetes Association, 2000)***.

In addition, defining the molecular genetics has shown that there are marked differences between genetic subgroups within these old broad categories making it much more appropriate to use the genetic subgroups, an approach that has been supported by the ADA and WHO in their guidelines on classification. There is great variation in the degree of hyperglycemia, need for insulin and risk for future complications ***(Ehtisham et al., 2004)***.

Neonatal diabetes

Insulin-requiring hyperglycemia in the first three months of life is known as neonatal diabetes mellitus. This rare condition (1 in 400,000 births) may be associated with intrauterine growth retardation ***(Metz et al., 2002; Von Muhlendahl and Herkenhoff, 1995)***. Approximately half of the cases are transient and have been associated with paternal isodisomy and other imprinting defects of chromosome 6 ***(Metz et al., 2002; Hermann et al., 2000)***. In patients with transient

neonatal diabetes mellitus, permanent diabetes may appear later in life ***(Gloyn et al., 2004)***. Permanent cases have been associated with pancreatic aplasia, activating mutations of KCNJ11, which is the gene encoding the ATP-Sensitive Potassium- Channel Subunit Kir6.2 (7p15-p13) ***(Massa et al., 2005)***, mutations of the Insulin Promoter Factor-1 (chromosome 7) in which there is pancreatic aplasia, complete glucokinase deficiency (chromosome 7) ***(Njolstad et al., 2001)***, mutations of the FOXP3 gene (T cell regulatory gene) as part of the IPEX syndrome ***(Bennett et al., 2001).***

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterised by progressive non-autoimmune beta-cell failure. Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. Although several mutations have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 in the mitochondrial tRNA (leu(UUR)) gene ***(Craig et al., 2009)***.

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Cystic fibrosis and diabetes

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Cystic Fibrosis related diabetes (CFRD) is primarily due to insulin deficiency, but insulin resistance during acute illness, secondary to infections and medications (bronchodilators and glucocorticoids), may also contribute to impaired glucose

tolerance and diabetes. CFRD tends to occur late in the disease, typically in adolescence and early adulthood. Cirrhosis, if present, may contribute to insulin resistance. The onset of CFRD is a poor prognostic sign, and is associated with increased morbidity and mortality. Poorly controlled diabetes will interfere with immune responses to infection and promote catabolism ***(Moran et al., 2009)***.

Genetic syndromes associated with diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus ***(World Health Organisation, 1999)***. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy ***(Barrett et al., 1995)***. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness.

Endocrinopathies

Several hormones (e.g., growth hormone, cortisol, glucagon, and epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with