

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by T-cell mediated destruction of the pancreatic B-cells, resulting in insulin deficiency and elevated blood glucose levels (*Daneman, 2006*).

The increasing incidence of type 1 diabetes in many countries challenges health systems because the disease is presently incurable with no known method of prevention (*James et al., 2014*). Around 490,100 children live with the disease worldwide, with incidence estimated to be increasing in children under 15 years by 2.8% per year (*Catanzariti et al., 2009*). This trend is particularly worrying because type 1 diabetes increases mortality and morbidity population-wide (*James et al., 2014*).

Vascular co-morbid diseases include retinopathy, which may cause reduced vision and blindness, and nephropathy, which may result in renal failure and require dialysis or kidney transplantation. This is in addition to hypertension, which is linked to peripheral, cardio- and cerebrovascular disease, the end points of which are limb amputations, cardiac failure, stroke and sudden death. As vascular complications curtail both life expectancy and quality of life (*Marshall and Flyvbjerg, 2009*) development at younger ages when people are typically establishing careers and families is particularly detrimental (*James et al., 2014*).

Atherosclerosis is the most common form of cardiovascular disease, and its pathological changes mainly involve large and medium-sized arteries, showing the lipids deposition and calcification in the intima (*Isoda et al., 2003*). Recent improvements in imaging technology (increased resolution and accuracy) have identified early vascular changes that can be assessed noninvasively using ultrasound (*Järvisalo et al., 2001*). Carotid intima media thickness (CIMT) is a simple, non-invasive, sensitive, screening tool for the assessment of atherosclerosis risk/prognosis in type 2 diabetic patients (*Kota et al., 2013*) but there are limited studies evaluating its role in type 1 diabetes in developing countries (*Gupta et al., 2013; Adly et al., 2014*). Autopsy studies, however, have shown that the first atherosclerotic lesions actually begin to develop in the abdominal aorta. Because it is now possible to visualize the abdominal aorta and accurately assess its wall thickness i.e. aortic intima media thickness (AIMT), measuring AIMT might provide a better index of preclinical atherosclerosis in high-risk children than CIMT (*Järvisalo et al., 2001*).

Angiopoietins are growth factors that promote angiogenesis together with vascular endothelial growth factor (VEGF) (*Gale et al., 2002; Resusch et al., 2001*). Angiopoietin-2 (Ang-2) is expressed primarily in the vascular endothelium at sites of vascular remodeling (*Maisonpierre et al., 1997*). Ang-2 acts by binding to the endothelium-specific receptor tyrosine

kinase 2 (Tie-2).The Ang/Tie system tightly controls the endothelial phenotype during angiogenesis and vascular inflammation in a unique fashion (*Rasul et al., 2011*).

Ang-2 appears to have an antagonistic effect. It acts as a competitive inhibitor of Ang-1 for Tie-2 binding, thereby inhibiting Ang-1/Tie-2 signaling (*Peters, 1998*).Ang-2 promotes also VEGF induced neovascularization (*Rasul et al., 2011*).

Growing evidence suggests an involvement of Ang-2 and its receptor Tie-2in the pathophysiology of different vascular and inflammatory diseases such as arteriosclerosis (*Marti and Risau, 1999*), hypertension (*Nader et al., 2005*),idiopathic pulmonary arterial hypertension (*Kumpers et al., 2010*), chronic kidney disease (*David et al., 2010*)and rheumatoid arthritis (*DeBusk et al., 2003*).Type 2 diabetes is associated with increased levels of Ang-2 and soluble Tie-2 (sTie-2) (*Rasul et al., 2011*). However, up till now, there are no published data on serum levels of Ang-2 in patients with type 1 diabetes mellitus and its relation to vascular structure in those patients remains to be fully elucidated.

AIM OF THE WORK

The aim of this study was to determine angiotensin-converting enzyme-2 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, glycemic control as well as carotid and aortic intima media thickness as index for subclinical atherosclerosis.

Chapter 1**TYPE 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 (*American Diabetes Association (ADA), 2014*).

The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic β -cell damage (type 1 DM), and those that are a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β -cell impairment (type 2 DM) (*Alemzadeh and Ali, 2011*).

Type 1 diabetes mellitus (T1DM) is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack (*Rother, 2007*).

Type 1 DM is the most common metabolic disease in childhood. Incidence rate varies greatly between different countries, within countries, and between different ethnic populations. The incidence of Type 1 DM increased worldwide in the closing decades of the 20th century. Steep rises in the age group under 5 years has been recorded recently (*Ismaeel et al., 2008*).

Type 1 diabetes is an important risk factor for cardiovascular events. Individuals with diabetes have 2-fold to 4-fold increased risk of developing atherosclerotic diseases, observations from postmortem studies have indicated that atherosclerosis in young adults is associated with the prediabetic state. Therefore, patients with type 1 diabetes mellitus in childhood may be at high risk of developing subsequent cardiovascular disease (*Järvisalo et al., 2004*).

Classification:

WHO classified DM into clinical types (normoglycemia, Impaired Glucose Tolerance (IGT)/ Impaired Fasting Glucose (IFG), diabetes) and etiological types (Table 1).

Table (1): Etiological classification of diabetes mellitus.

<p>Type I-DM: (β-cell destruction, usually leading to absolute insulin deficiency) A. Immune mediated B. Idiopathic.</p>	<p>II. Type II-DM: (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)</p>
<p>III. Other specific types</p>	
<p>A. Genetic defects of β-cell function 1. MODY 3 (Chromosome 12, HNF1α) 2. MODY 1 (Chromosome 20 HNF-4α) 3. MODY 2 (Chromosome 7, glucokinase) 4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, NeuroD1; MODY 7: Chromosome 9, carboxyl ester lipase) 5. Transient neonatal diabetes 6. Permanent neonatal diabetes 7. Mitochondrial DNA 8. Others</p>	<p>B. Genetic defects in insulin action 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipotrophic diabetes 5. Others</p>
<p>C. Diseases of the exocrine pancreas 1. Pancreatitis 2. Trauma / pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Haemochromatosis 6. Fibrocalculous pancreatopathy 7. Others</p>	<p>D. Endocrinopathies 1. Acromegaly 2. Cushing’s syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others</p>
<p>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</p>	<p>F. Infections 1. Congenital rubella 2. Cytomegalovirus 3. Others</p>
<p>G. Uncommon forms of immune-mediated diabetes 1. “Stiff-man” syndrome 2. Anti-insulin receptor antibodies 3. Others</p>	<p>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</p>
<p>IV. Gestational Diabetes.</p>	

(ADA, 2014)

MODY: Maturity onset diabetes of the young, **HNF-4 α :** Hepatocyte Nuclear Factor, **NeuroD1:** Neurogenic differentiation.

The vast majorities of cases with diabetes fall into two etiopathogenetic categories; type 1 and type 2 diabetes mellitus (*ADA, 2007*). The comparison between both types is presented in Table 2.

Table (2): 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
Clinical presentation	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except Glucokinase and neonatal Diabetes
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*)

Type 1 is further classified to the following subtypes:

▪ **Type 1a (The autoimmune form):**

This form of diabetes, which accounts for only 5–10% of those with diabetes, previously known insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of pancreatic β -cells representing about 90% of type 1 cases in Europe. The presence of other autoimmune disorders is highly raised (*ADA, 2012*).

▪ **Type 1b (The idiopathic form):**

The cause of insulin deficiency is not related to autoimmunity and it remains undefined. These cases are categorized as type 1b or idiopathic type 1 DM and are relatively more common in African and Asian population. This category is heterogeneous, may be caused by different mechanisms in different populations, and remain poorly understood at this time (*Umpierrez et al., 2006*).

▪ **Type 1c:**

It is the fulminant type 1 diabetes mellitus (FT1DM), it was first reported by *Imagawa et al. (2000)* and it is a unique subtype of diabetes. It is characterized by a short clinical history, before the first acute metabolic decompensation with impairment of beta and alpha cells of the pancreatic islet and no autoimmune etiology (*Arai et al., 2012*).

Epidemiology:

With 1 in 300 affected worldwide (*Vehic et al., 2011*). Differences in disease prevalence and changes in incidence rates suggest that a combination of multiple genetic and environmental factors contribute to T1DM risk (*Haller et al., 2005*). The incidence of type 1 diabetes varies by geography. The estimated prevalence of T1DM in children and adolescents is 0.38/1000 in Egypt (*Salem et al., 2010*).

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 (*Dejckhamron et al., 2007*).

Over the past 30 years, the ability to predict the development of T1DM has improved dramatically with the combined use of genetic, autoantibody, and metabolic markers (*Haller et al., 2005*).

The rising incidence and decreasing age at diagnosis of type 1 diabetes is accounted for by the impact of environment on children with lower-risk HLA class II genes, who previously would not have developed type 1 diabetes in childhood (*Fourlanos et al., 2008*).

Because clinical T1DM typically does not present until approximately 80% to 90% of the beta cells have been destroyed, there is a marked gap between the onset of autoimmunity and the onset of diabetes (*Haller et al., 2005*).

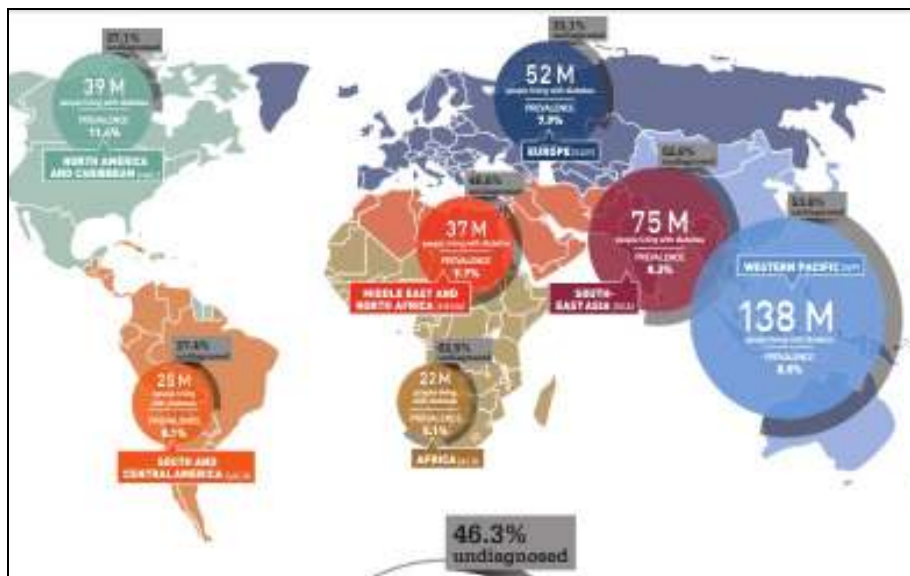


Figure (1): Global diabetes prevalence (*IDF Diabetes Atlas, 2014*)

Among Eastern Mediterranean and Middle Eastern countries, the largest contribution to the total number of estimated childhood T1DM cases comes from Egypt which accounts for about a quarter of the region's total. The incidence varies between 1/100 000 per year (Pakistan) and 8/100 000 per year (Egypt) in children under the age of 15 years (*Soltész et al., 2006*) (Figure 1).

An Egyptian 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.

Risk factors

Unlike with T2DM, few risk factors have been identified for T1DM. Additionally, no risk factor has been shown to be singly responsible for the development of T1DM, suggesting that the disease arises as the result of a number of triggers. A patient's risk for eventually developing T1DM can be quantified by measuring levels of specific biomarkers, molecules indicating that an autoimmune reaction against the pancreatic islet cells is occurring. For example, the presence of antibodies against the pancreatic islet cells, or directed against insulin itself, are both suggestive of an autoimmune reaction. Also, as the understanding of genetic factors that lead to T1DM increases, gene tests may help to identify patients likely to develop the disease (*Atkinson, 2012*).

Family history

One major risk factor for the development of T1DM is family history. Individuals with a first-degree relative (i.e., parent, child, or sibling) diagnosed with T1DM are at a significantly greater likelihood of developing the disease themselves (*Atkinson, 2012*).

Although more than 85% of type 1 diabetes occurs in individuals with no previous first degree family history, the risk among first degree relatives is about 15 times higher than in the general population (*Delli et al., 2010*)

On average (Table 3):

If a mother has the condition, the risk of developing it is about 2–4 per cent

If a father has the condition, the risk of developing it is about 6–9 per cent

If both parents have the condition, the risk of developing it is up to 30 per cent

If a brother or sister develops the condition, the risk of developing it is 10 per cent (rising to 10–19 per cent for a non-identical twin and 30–70 per cent for an identical twin) (*Delli et al., 2010*).

Table (3): Risk of type 1 diabetes by affected family member

Affected family member	Risk of developing type 1 diabetes
Mother	2-4%
Father	6-9%
Both parents	30%
Sibling	10%
Non-identical twin	10-19%
Identical twin	30-70%

(*Delli et al., 2010*)

Gender

Unlike many other autoimmune diseases, where females are more at risk of disease, boys and girls under age 15 are diagnosed with type 1 diabetes at relatively equal rates. Some populations with a high incidence tend to have more males than females with type 1, while some with low incidence show more females than males, although this varies among studies. In people of European descent diagnosed at ages 15-40, however, there is a clear male predominance: more men than women are diagnosed with type 1 diabetes at these older ages (*Soltesz et al., 2007*).

Age

On average, in children under age 15, type 1 diabetes incidence increases as a child gets older. In other words, a person 10-14 years old has a higher risk of developing type 1 diabetes, someone 5-9 years old has a middle risk, and someone 0-4 years old has a lower risk. Someone 10-14 has about twice the risk of developing type 1 diabetes as someone under 5. This trend generally does not vary by gender. Overall, and especially in Europe, however, the rates of increase, however, have been highest in children under age 5, with a 4% annual increase in this age group (*Diamond Project Group, 2006*).

Seasonal variation

A seasonal pattern in type 1 diabetes diagnosis has been seen in some countries, with more people diagnosed during the winter months. The pattern is most apparent in countries with greater differences in summer vs. winter temperatures (*Soltész et al., 2007*).

Environmental factors

Dietary components are one example of environmental factors that may lead to the development of T1DM. Among these dietary factors, short duration of breastfeeding and early introduction of solid food and cow's milk to infants are leading candidates. Short breastfeeding duration was suggested as a possible risk factor in the wake of evidence showing that breastfeeding for less than one year and/or a lack of breastfeeding increases the risk for development of T1DM later in life. The evidence virus itself may target these cells, damaging them and rendering them incapable of effectively producing insulin. Viruses suggested to play a role in the pathogenesis of T1DM include the Epstein-Barr virus, coxsackievirus, mumps virus, and cytomegalovirus (*Galleri et al., 2012*).for early introduction of solid food and cow's milk as risk factors is more controversial, and some studies show no evidence to support this (*Patelarou et al., 2012*).