INTRODUCTION

Type-2 diabetes mellitus (T2DM) is the leading cause of cardiovascular morbidity and mortality worldwide. Poor glucose control, hypertension, and dyslipidemia are the main factors that increase the risk of atherosclerotic disease in T2DM ***(Beckman et al., 2002).***

Inflammation and endothelial dysfunction initiate the pathogenesis of atherosclerosis, from the earliest steps of monocyte recruitment to the complicated phase of plaque rupture ***(Bäck et al., 2015)***. Being the most abundant cell type in atherosclerotic plaques, Macrophages are present in all phases of atherogenesis, and are markers of atherosclerotic plaque formation ***(Cochain and Zernecke, 2015).***

Chitotriosidase, also named chitinase-1 (CHIT1), belongs to the 18 family of chitinases which is unexpectedly discovered in humans in the 1990s ***(Guan et al., 2009).***

The exact function of human CHIT1 remains unclear, but its participation in process of inflammation and immune defense is postulated ***(van Eijk et al., 2005).***

Chitotriosidase has been implicated in the pathogenesis of many human diseases such as bronchial asthma, chronic obstructive pulmonary disease (COPD) ***(Kim et al., 2013)*** non alcoholic fatty liver disease ***(Di Rosa et al., 2007),*** and neuro-degenerative disorders like Alzheimer's disease and

amyotrophic lateral sclerosis ***(Rosen et al., 2014).*** CHIT1 has been included also as one of the secreted biomarkers for Gaucher's disease ***(Hollak et al., 1994).***

The elevation of CHIT1 in these patients may reflect a particular state of activation of macrophages ***(Boot et al., 2004).*** In a healthy population, CHIT1 activity is very low and originates in circulating polymorphonuclear cells ***(Boot et al., 1998)***. Conversely, during the development of acute/chronic inflammatory disorders, the enzymatic activity of CHIT1 increases significantly ***(Malaguarnera, 2006).***

Based on this data, some authors have postulated participation of chitotriosidase in the development of atherosclerosis, which creates a possible link to the course of type 2 diabetes (T2D) ***(Artieda et al., 2006).***

AIM OF THE WORK

To study the relationship between Chitotriosidase level in patients with Type 2 Diabetes Mellitus and the development of atherosclerosis.

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, 2017).***

Diabetes Mellitus (DM) is a recognized pandemic and treatment costs of DM and its complications are a major burden on healthcare systems throughout the world. Diabetic vasculopathy (DV) is the most important consequence of chronic hyperglycemia, in patients with DM ***(Conte et al., 2015).***

Epidemiology

Diabetes mellitus is one of the most challenging health problems in the 21st century. 425 million people around the world had diabetes in 2017, by 2045 this will have risen to 693 million 18-99 years. 629 million of people 20-79 years, will have diabetes. The largest increases will take place in regions where economies are moving from low income to middle income levels.

Diabetes estimates have been on the rise for several decades. More than one-third of diabetes cases are estimated to result from population growth and ageing, 28% from an increase in age-specific prevalences and 32% from the interaction of these two ***(IDF, 2017).*** The increase in rates in developing countries may be explained also by the trend of urbanization and lifestyle changes, Perhaps most importantly a "Western-style" diet. This has suggested an environmental effect ***(Wild et al., 2004).***

Globally diabetes results in 727 billion USD being spent yearly by people with diabetes only on healthcare, which corresponds to one for every eight dollars spent on healthcare ***(IDF, 2017).***

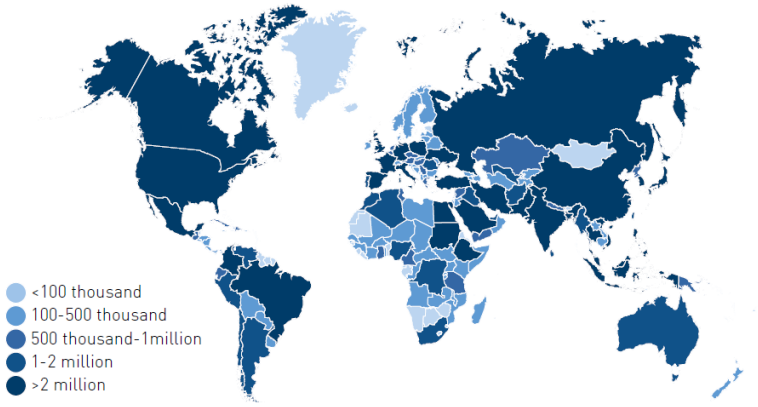

Figure (1): Estimated total number of adults (20-79 years) living with diabetes, 2017 ***(IDF, 2017).***

Egypt is the 8th country worldwide regarding number of people with diabetes ***(IDF, 2017)***. Also, DM is the eleventh most important cause of premature mortality in Egypt and is

responsible for 2.4% of all years of life lost. Similarly, diabetes is the sixth most important cause of disability burden in Egypt ***(Arafa and Amin, 2010).***

About 51.8% of all deaths in adults before 60 in the Middle East and North Africa are attributable to diabetes. Early death from diabetes may be a result of the rapidly changing environments and lifestyles of the region, late diagnosis, and health systems ***(IDF, 2017).***

Classification of Diabetes Mellitus

1. Type 1 diabetes (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of beta cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation) ***(ADA, 2018).***

Type 1 diabetes mellitus (T1DM)

Previously called "insulin- dependent diabetes. It accounts for 5-10% of diabetes and is due to cellular mediated autoimmune destruction of the pancreatic Beta cells ***(Dabelea et al., 2014).***

Autoimmune markers include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to Glutamic Acid Decarboxylase (GAD) (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2b, and autoantibodies to zinc transporter 8 (ZnT8). Type 1 DM is defined by the presence of one or more of these autoimmune markers ***(Ziegler el al., 2013).***

The disease has strong human leukocyte antigen (HLA) associations, with linkage to the DQA and DQB genes. The rate of beta-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults) ***(Sorensen et al., 2013).***

Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient beta-cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter

stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide ***(Sosenko et al., 2013).***

Type 2 diabetes mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) ranks highly on the international health agenda as a global pandemic and as a threat to human health and global economies. The number of people with T2DM worldwide has more than doubled during the past 20 years) ***(Zimmet et al., 2014).***

Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia ***(Unger et al., 2010).***

Table (1): Clinical features that commonly distinguish T1DM and T2DM ***(ADA, 2013).***

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Age at onset (years)	Majority <25, but may occur at any age	Typically >25 but incidence is increasing in adolescents due to increasing rates of obesity in this age group
Symptoms at presentation	Polyuria, polydipsia, fatigue	Majority asymptomatic
Phenotype	Thin	>90 % overweight
Autoantibodies	Present	Absent
Insulin dependant	Yes	Not initially
Insulin sensitivity	Normal when controlled	Decreased
Family history of diabetes	Infrequent (5–10 %)	Frequent (75–90 %)
Risk of diabetic ketoacidosis	High	Low

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There are several other less common forms of diabetes. Latent autoimmune diabetes of adults (LADA) is a term used to describe the development of diabetes-associated antibodies and diabetes onset in older adults. It is thought to account for 2–12% of all diabetes cases ***(Guglielmi et al., 2012)***.

Maturity onset diabetes of the young (MODY) is a heterogeneous group of disorders caused by a mutation in one of the six genes essential for β-cell function and accounts for

1 % of diabetes cases presented in adolescence or young adulthood with mild asymptomatic hyperglycemia. It can be differentiated from T2D by the presence of a strong family history of diabetes with an apparent autosomal dominant pattern of inheritance, milder hyperglycemia, and often lack of obesity. Genetic testing should be performed in cases with a high index of suspicion ***(Kavvoura and Owen, 2012)***.

Etiology and pathophysiology of T2DM

For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycemia.

A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

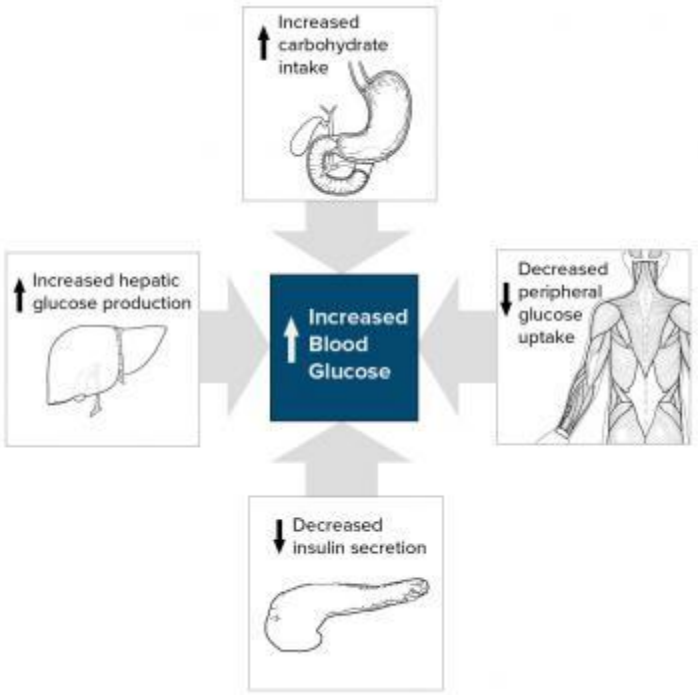

Figure (2): Simplified scheme for the pathophysiology of type 2 diabetes mellitus.(https://emedicine.medscape.com/article/117853-overview)

With prolonged diabetes, atrophy of the pancreas may occur. A study by Philippe et al used computed tomography (CT) scan findings, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic activity in individuals with a median 15-year history of diabetes mellitus (range, 5-26 years). This may also explain the associated exocrine deficiency seen in prolonged diabetes ***(Philippe et al., 2011).***

A- Beta-cell dysfunction

Beta-cell dysfunction is a major factor across the spectrum of prediabetes to diabetes. A study of obese adolescents by Bacha et al confirms that: Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance ***(Bacha et al., 2010).***

B- Insulin resistance

In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first. Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

During the induction of insulin resistance (such as occurs with a high-calorie diet, steroid administration, or physical inactivity), increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance. However, the postprandial glucagonlike peptide-1 (GLP-1) response is unaltered ***(Hansen et al., 2011).***

C- Genomic factors

Genome-wide association studies of single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants that are associated with beta-cell function and insulin

resistance. Some of these SNPs appear to increase the risk for type 2 diabetes. Over 40 independent loci demonstrating an association with an increased risk for type 2 diabetes have been shown ***(Wheeler et al., 2011).***

A subset of the most potent are shared below ***(Billings et al., 2010):***

- Decreased beta-cell responsiveness, leading to impaired insulin processing and decreased insulin secretion (*TCF7L2)*
- Lowered early glucose-stimulated insulin release (*MTNR1B, FADS1, DGKB, GCK*)
- Altered metabolism of unsaturated fatty acids (*FSADS1*)
- Dysregulation of fat metabolism (*PPARG*)
- Inhibition of serum glucose release (*KCNJ11*)
- Increased adiposity and insulin resistance (*FTO* and *IGF2BP2*)
- Control of the development of pancreatic structures, including beta-islet cells (*HHEX*)
- Transport of zinc into the beta-islet cells, which influences the production and secretion of insulin (*SLC30A8*)
- Survival and function of beta-islet cells (*WFS1*)

D- Environmental factors

Aging, obesity, insufficient energy consumption, alcohol drinking and smoking are independent risk factors of T2DM pathogenesis. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance. Even mild obesity causes a 4- to 5-fold increase in the risk of developing T2DM, if accompanied by the increase in visceral fat mass ***(Kaku, 2010)***.

Diagnosis of diabetes mellitus

Signs and symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria, polydipsia, and polyphagia. Symptoms may develop rapidly (weeks or months) in type 1DM, while they usually develop much more slowly in type 2 DM ***(Cooke and Plotnick, 2009).***

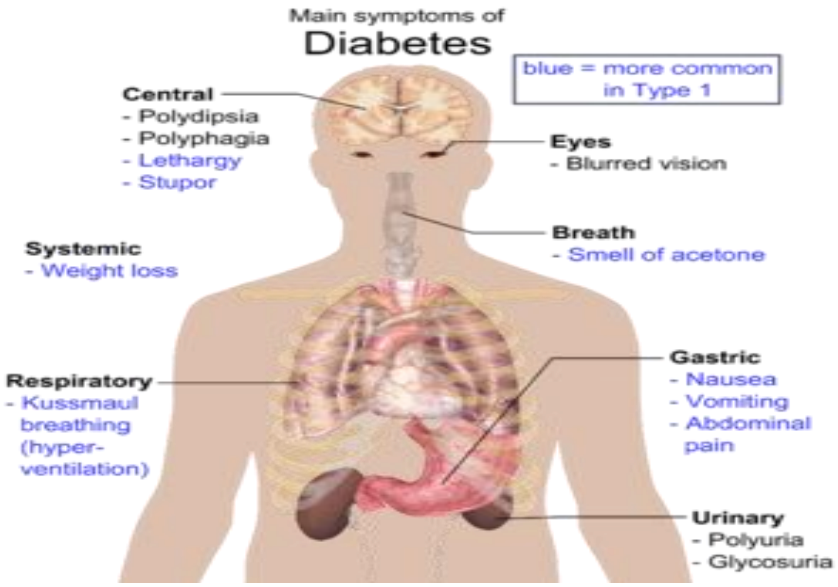

Figure (3): Overview of the most significant symptoms of diabetes.(https://en.wikipedia.org/wiki/Diabetes_mellitus)

Diagnostic criteria by the American Diabetes Association (ADA) include the following ***(ADA, 2018):***

- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, *or*
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), *or*
- A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Whether a hemoglobin A1c (HbA1c) level of 6.5% or higher should be a primary diagnostic criterion or an optional criterion remains a point of controversy.

Indications for diabetes screening in asymptomatic adults includes the following ***(Barnea-Goraly et al., 2014).***

- Sustained blood pressure >135/80 mm Hg
- Overweight and 1 or more other risk factors for diabetes (eg, first-degree relative with diabetes, BP >140/90 mm Hg, and HDL < 35 mg/dL and/or triglyceride level >250 mg/dL)
- ADA recommends screening at age 45 years in the absence of the above criteria